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A 67-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. She was diagnosed with diabetes 6 months ago. Lifestyle modification was initially advised, but the patient had no significant glycemic improvement. One month ago, the patient was started on metformin, to which she has been adherent; however, she has been experiencing abdominal discomfort and diarrhea attributed to the therapy. She has no other medical conditions. BMI is 28 kg/m^2. Physical examination is unremarkable. Laboratory tests show hemoglobin A1c is 8.2%. After further discussion, metformin is discontinued and glyburide is prescribed. Compared to metformin, this new therapy is most likely to increase the risk of which of the following?

A. Acute pancreatitis

B. Renal dysfunction

C. Symptomatic hypoglycemia

D. Vitamin B_{12} deficiency

E. Vulvovaginal candidiasis

Submit

A 67-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. She was diagnosed with diabetes 6 months ago. Lifestyle modification was initially advised, but the patient had no significant glycemic improvement. One month ago, the patient was started on metformin, to which she has been adherent; however, she has been experiencing abdominal discomfort and diarrhea attributed to the therapy. She has no other medical conditions. BMI is 28 kg/m^2. Physical examination is unremarkable. Laboratory tests show hemoglobin A1c is 8.2%. After further discussion, metformin is discontinued and glyburide is prescribed. Compared to metformin, this new therapy is most likely to increase the risk of which of the following?

- A. Acute pancreatitis (5%)
- B. Renal dysfunction (3%)
- ✓ C. Symptomatic hypoglycemia (88%)
- D. Vitamin B_{12} deficiency (0%)
- E. Vulvovaginal candidiasis (1%)

Omitted
Correct answer
C

88%
Answered correctly

03 secs
Time Spent

04/27/2020
Last Updated

Explanation

Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	Mechanism of action	Side effects
Insulin		

Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	**Mechanism of action**	**Side effects**
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
Biguanides • Metformin	Stimulate AMPK & inhibit mitochondrial gluconeogenesis, ↓ hepatic glucose production & ↑ peripheral glucose uptake	• Diarrhea • Lactic acidosis
Thiazolidinediones • Pioglitazone	Activate transcription regulator PPAR-γ, ↓ insulin resistance	• Fluid retention/heart failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
α-glucosidase inhibitors • Acarbose • Miglitol	↓ Intestinal disaccharide absorption	• Diarrhea • Flatulence
SGLT2 inhibitors		Urinary tract

DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
α-glucosidase inhibitors • Acarbose • Miglitol	↓ Intestinal disaccharide absorption	• Diarrhea • Flatulence
SGLT2 inhibitors • Canagliflozin • Dapagliflozin	↑ Renal glucose excretion	• Urinary tract infections • Hypotension
AMPK = adenosine monophosphate–activated protein kinase; **DPP4** = dipeptidyl peptidase-4; **GIP** = gastric inhibitory polypeptide; **GLP-1** = glucagonlike peptide-1; **K_{ATP}** = ATP-sensitive potassium; **PPAR-γ** = peroxisome proliferator–activated receptor γ; **SGLT2** = sodium-glucose cotransporter 2.		

Metformin is the preferred initial medication for most patients with type 2 diabetes due to its overall efficacy and lack of hypoglycemia when used in monotherapy. However, metformin can cause bothersome gastrointestinal effects (eg, nausea, diarrhea), which may be severe enough to warrant a change in therapy.

Sulfonylureas are second-line agents that are frequently used as add-on therapy or as a replacement for metformin. **Sulfonylureas** inhibit the **ATP-sensitive potassium channel** on the pancreatic beta cell membrane, inducing depolarization and L-type calcium channel opening. The increased Ca^{2+} influx stimulates beta cell **insulin release** independent of blood glucose concentrations. Meglitinides (eg, repaglinide, nateglinide) are short-acting drugs that are functionally similar to sulfonylureas.

Sulfonylureas continue to stimulate insulin secretion, even when blood glucose levels are normal and can therefore cause **hypoglycemia**. Hypoglycemia due to sulfonylureas can be induced by exercise, missed meals, acute illness, or initiation of additional antidiabetic medications. Longer-acting sulfonylureas (eg, glyburide) are more prone to causing hypoglycemia than shorter-acting drugs (eg, glipizide).

(Choice A) Glucagonlike polypeptide-1 (GLP-1) regulates glucose by slowing gastric emptying and increasing insulin release. Pharmacologic

glucose cotransporter 2.

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(Choice A) Glucagonlike polypeptide-1 (GLP-1) regulates glucose by slowing gastric emptying and increasing insulin release. Pharmacologic GLP-1 agonists (eg, exenatide) lower blood glucose and promote weight loss. Acute pancreatitis is an uncommon but serious adverse effect.

(Choice B) Renal dysfunction can occur with sodium-glucose cotransporter 2 (SGLT2) inhibitors due to excessive osmotic diuresis, but it is not a common adverse effect of sulfonylureas. However, preexisting renal impairment can increase the risk of hypoglycemia due to sulfonylureas and can increase the risk of lactic acidosis due to metformin.

(Choice D) Metformin can decrease absorption of vitamin B_{12}, leading to B_{12} deficiency in long-term use. Sulfonylureas do not have a significant effect on vitamin B_{12} metabolism.

(Choice E) SGLT2 inhibitors (eg, dapagliflozin) decrease renal reabsorption of glucose, leading to increased urinary glucose loss and lower blood glucose levels. The excess glucose in the urine can increase the risk of urinary tract infections and vulvovaginal candidiasis. They can also cause hypotension due to osmotic diuresis.

Educational objective:
Sulfonylureas inhibit the ATP-sensitive potassium channel on the pancreatic beta cell membrane, inducing depolarization and L-type calcium channel opening. The increased Ca^{2+} influx stimulates beta cell insulin release independent of blood glucose concentrations. Sulfonylureas

ATP-sensitive potassium channel on the pancreatic beta cell membrane, inducing depolarization and L-type calcium channel opening. The increased Ca^{2+} influx stimulates beta cell **insulin release** independent of blood glucose concentrations. Meglitinides (eg, repaglinide, nateglinide) are short-acting drugs that are functionally similar to sulfonylureas.

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Educational objective:
Sulfonylureas inhibit the ATP-sensitive potassium channel on the pancreatic beta cell membrane, inducing depolarization and L-type calcium channel opening. The increased Ca^{2+} influx stimulates beta cell insulin release independent of blood glucose concentrations. Sulfonylureas stimulate insulin secretion, even when blood glucose levels are normal, which can lead to hypoglycemia.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 62-year-old woman is brought to the emergency department after a fall and is found to have a left femoral neck fracture. The patient is admitted to the hospital, and a hip arthroplasty is planned. Medical history is significant for long-standing type 2 diabetes mellitus, hypertension, hyperlipidemia, and migraines. While hospitalized, the patient receives a combination of long- and short-acting insulin for diabetes management. On the morning of surgery, fasting blood glucose level is 42 mg/dL. The patient is awake and alert and says she feels hungry but has no other symptoms of hypoglycemia. Concurrent use of which of the following medications best explains this finding?

- A. Atorvastatin
- B. Doxazosin
- C. Hydrochlorothiazide
- D. Losartan
- E. Propranolol
- F. Verapamil

Submit

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- A. Atorvastatin (6%)
- B. Doxazosin (6%)
- C. Hydrochlorothiazide (16%)
- D. Losartan (4%)
- ✓ E. Propranolol (63%)
- F. Verapamil (2%)

Omitted
Correct answer
E

63%
Answered correctly

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Time Spent

06/07/2020
Last Updated

Explanation

Sympathetic system neurotransmitters

CNS

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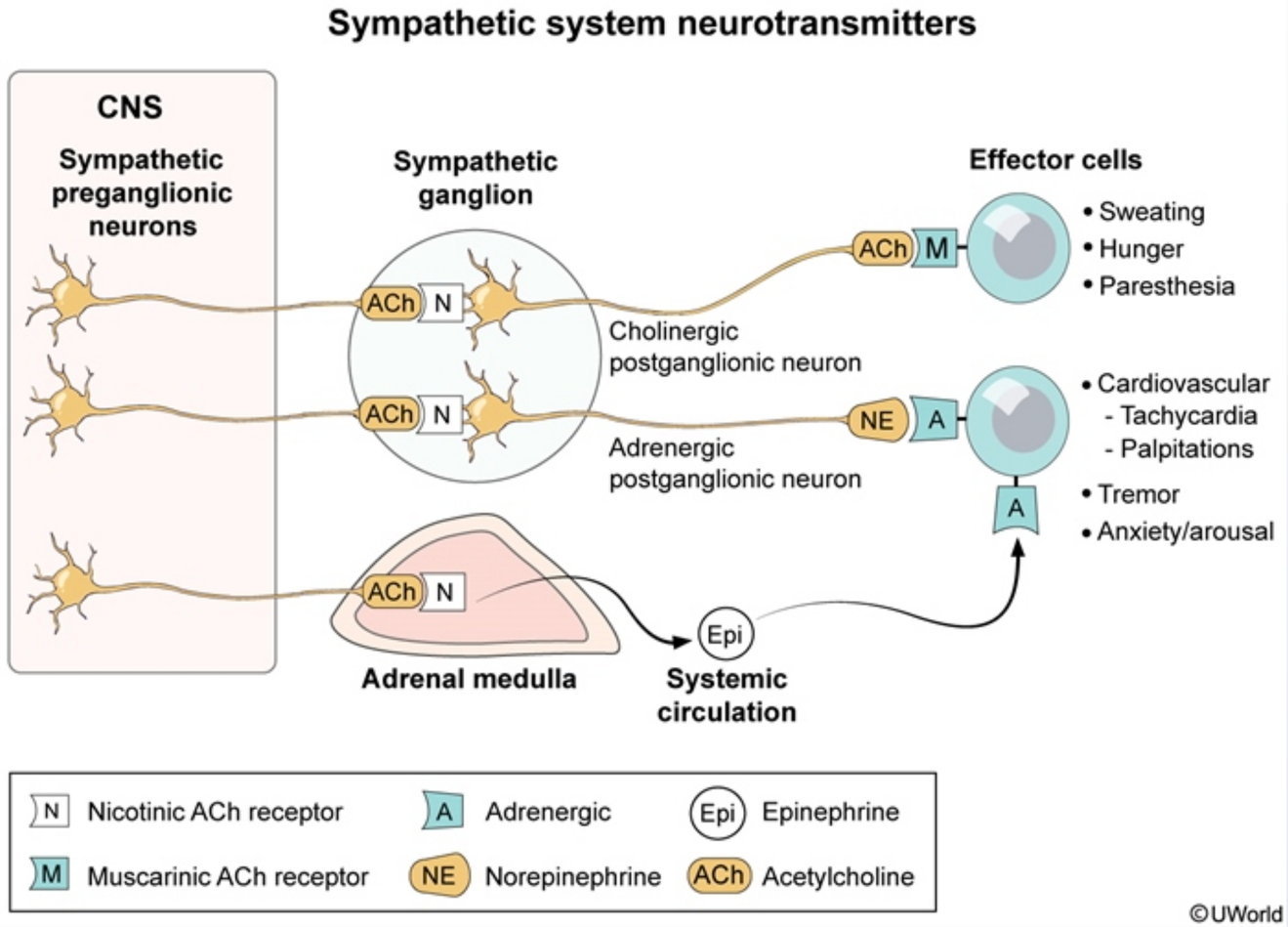

Prolonged hypoglycemia can lead to irreversible neurologic deficits and death. To prevent injury, counterregulatory systems raise blood glucose in response to hypoglycemia via sympathetic nervous system activation (ie, norepinephrine/**epinephrine** release) and increase secretion of **glucagon**, cortisol, and growth hormone.

Symptoms of hypoglycemia fall into 2 general categories: neurogenic (autonomic) and neuroglycopenic.

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Symptoms of hypoglycemia fall into 2 general categories: neurogenic (autonomic) and neuroglycopenic.

- **Neurogenic symptoms** are mediated via norepinephrine/epinephrine and acetylcholine release during sympathetic stimulation. Symptoms due to **norepinephrine/epinephrine** include tremulousness, tachycardia, and anxiety/arousal, whereas **acetylcholine** causes sweating, hunger, and paresthesias.
- **Neuroglycopenic symptoms** are due to inadequate availability of glucose in the CNS and include behavioral changes, confusion, visual disturbances, stupor, and seizures.

This patient has **reduced awareness** of hypoglycemia, likely due to the use of a **nonselective beta blocker** (eg, propranolol) for chronic treatment of migraines and/or hypertension. Nonselective beta blockers attenuate the norepinephrine/epinephrine-mediated symptoms of hypoglycemia, but cholinergic symptoms (eg, hunger) are unaffected. In addition, nonselective beta blockers can contribute to the severity of hypoglycemia; epinephrine stimulates hepatic gluconeogenesis and peripheral glycogenolysis, but this effect is diminished by nonselective beta blockers.

(Choices A and C) Statins (eg, atorvastatin) and hydrochlorothiazide can increase blood glucose levels but would not mask symptoms of hypoglycemia.

(Choice B) Insulin-secreting pancreatic beta cells have alpha-2 and beta-2 receptors; stimulation of alpha-2 receptors inhibits insulin secretion, whereas stimulation of beta-2 receptors increases insulin secretion. Doxazosin is a selective alpha-1 blocker and has no effect on glucose levels.

(Choices D and F) Angiotensin II receptor blockers (eg, losartan) and nondihydropyridine calcium channel blockers (eg, verapamil) do not mask the symptoms of hypoglycemia and have virtually no effect on glucose levels.

Educational objective:
Nonselective beta blockers exacerbate hypoglycemia and mask hypoglycemic symptoms mediated by norepinephrine/epinephrine.

References

- Glucose counterregulatory responses to hypoglycemia.

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Nonselective beta blockers exacerbate hypoglycemia and mask hypoglycemic symptoms mediated by norepinephrine/epinephrine.

References

- Glucose counterregulatory responses to hypoglycemia.

Pharmacology	Endocrine, Diabetes & Metabolism	Hypoglycemia
Subject	System	Topic

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A 42-year-old woman with Graves disease is hospitalized for elective total thyroidectomy. Her hyperthyroid symptoms have been controlled with methimazole and propranolol, but she still has a goiter. The patient has no other medical problems. She undergoes total thyroidectomy without any immediate operative complications and feels well the next day. Laboratory results are as follows:

Serum chemistry

Sodium	141 mEq/L
Potassium	4.4 mEq/L
Creatinine	0.8 mg/dL
Calcium	7.5 mg/dL

Preoperative electrolyte values were within normal limits. Which of the following medications should be started in this patient?

A. Alendronate
B. Calcitriol
C. Cinacalcet
D. Prednisone
E. Radioactive iodine
F. Sevelamer

Submit

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Potassium	4.4 mEq/L
Creatinine	0.8 mg/dL
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Preoperative electrolyte values were within normal limits. Which of the following medications should be started in this patient?

A. Alendronate (5%)
✓ B. Calcitriol (66%)
C. Cinacalcet (19%)
D. Prednisone (1%)
E. Radioactive iodine (2%)
F. Sevelamer (3%)

Omitted
Correct answer
B

66%
Answered correctly

02 secs
Time Spent

03/06/2020
Last Updated

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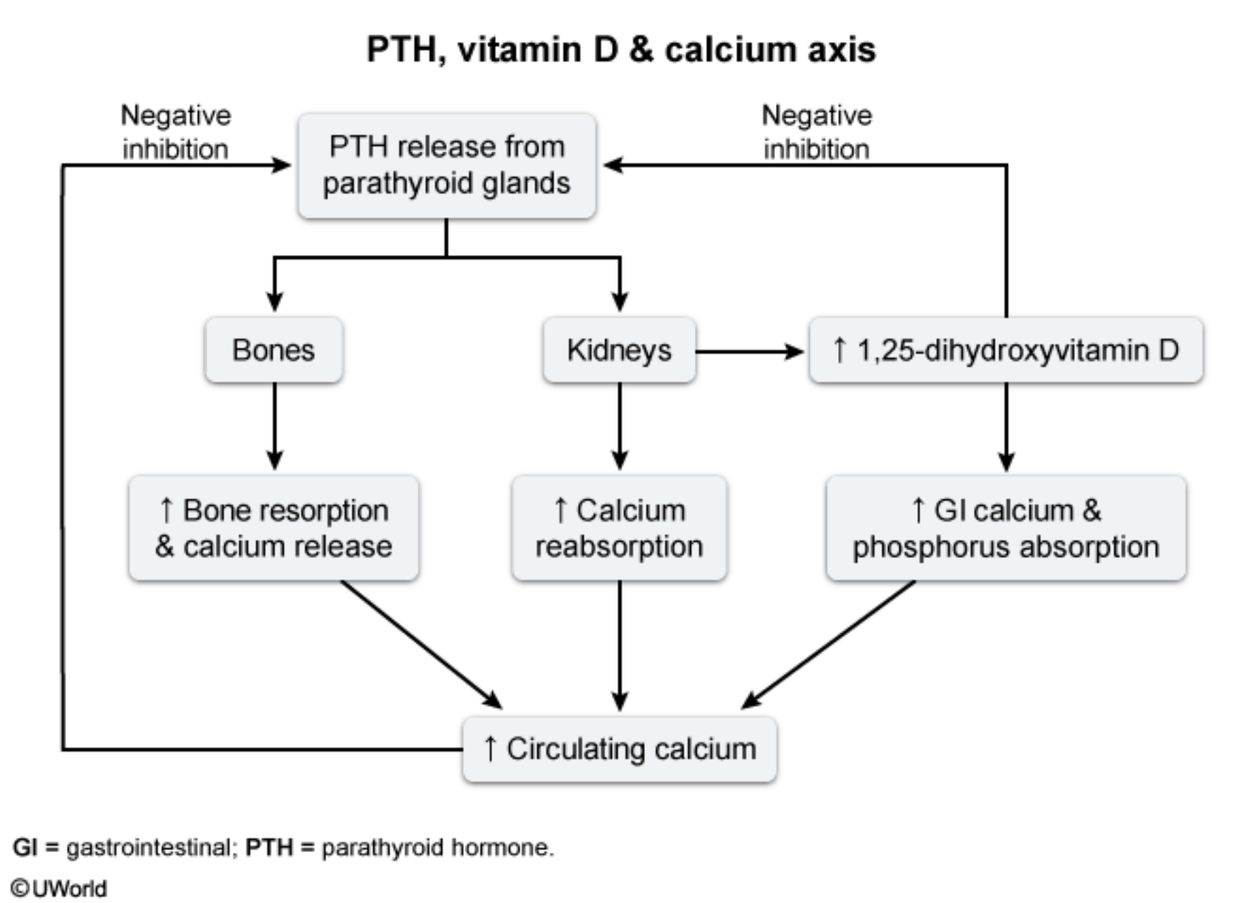

The **parathyroid glands** are relatively small and indistinct and can be **injured during thyroid surgery** due to direct trauma, devascularization, or inadvertent removal. Transient or permanent postoperative **hypoparathyroidism** can occur following thyroidectomy and cause clinically significant **hypocalcemia**. Patients may be asymptomatic initially but can develop paresthesias (of the lips, mouth, hands, and feet), muscle twitching, or cramps. Worsening hypocalcemia can lead to trismus or tetany with changes in mental status and generalized seizures.

Postoperative supplementation with oral calcium and vitamin D can be used to treat and prevent postoperative hypocalcemia. **Calcitriol**, the active form of vitamin D, should be chosen over calcidiol as the conversion of calcidiol to calcitriol is dependent on parathyroid hormone, and

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Postoperative supplementation with oral calcium and vitamin D can be used to treat and prevent postoperative hypocalcemia. **Calcitriol**, the active form of vitamin D, should be chosen over calcidiol as the conversion of calcidiol to calcitriol is dependent on parathyroid hormone, and patients with hypoparathyroidism can have inadequate production of calcitriol.

(Choice A) Alendronate is a bisphosphonate that inhibits osteoclast function. Bisphosphonates can worsen hypocalcemia by decreasing the release of calcium from bone.

(Choice C) Cinacalcet is a calcimimetic that allosterically activates the calcium-sensing receptor in the parathyroid gland, decreasing parathyroid hormone release. Cinacalcet is normally used for secondary hyperparathyroidism in patients on dialysis.

(Choice D) Glucocorticoids (eg, prednisone) can worsen hypocalcemia by decreasing expression of the vitamin D receptor.

(Choice E) The primary treatment modalities for Graves disease include antithyroid drugs (eg, methimazole), thyroidectomy, and radioiodine ablation. This patient has undergone definitive treatment with thyroidectomy and has no indication for radioiodine therapy.

(Choice F) Sevelamer is a nonabsorbable phosphate-binding polymer that decreases absorption of phosphate in the gastrointestinal tract, and is used to treat hyperphosphatemia in patients on dialysis. Calcium-based phosphate binders (eg, calcium carbonate, calcium acetate) frequently raise calcium levels, but sevelamer has a lesser effect on calcium and would not be adequate treatment for hypocalcemia.

Educational objective:
Postoperative hypoparathyroidism with resultant hypocalcemia is a common complication of thyroidectomy due to inadvertent injury or removal of the parathyroid glands. Postoperative supplementation with oral calcium and vitamin D can be used to treat and prevent postoperative hypocalcemia.

References

- Role of postoperative vitamin D and/or calcium routine supplementation in preventing hypocalcemia after thyroidectomy: a systematic review and meta-analysis.

A 45-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. The patient was diagnosed with diabetes 3 years ago after developing polyuria, polydipsia, and recurrent vulvovaginal candidiasis. She initially tried lifestyle changes but had no significant glycemic improvement and was started on metformin. The patient is adherent with her therapy and consumes a low-carbohydrate diet. Family history is significant for an osteoporotic fracture in her mother. Blood pressure is 134/86 mm Hg and pulse is 72/min. BMI is 33 kg/m^2. Physical examination shows no abnormalities. Laboratory results show a hemoglobin A1c of 8.2%. After further discussion, a sodium-glucose cotransporter-2 inhibitor is added to the patient's drug regimen. Which of the following is the most likely additional effect of the newly prescribed medication?

- A. Decreased blood pressure
- B. Decreased genitourinary infections
- C. Increased bone mineral density
- D. Increased fluid retention
- E. Increased postprandial satiety

Submit

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- ✓ A. Decreased blood pressure (73%)
- B. Decreased genitourinary infections (4%)
- C. Increased bone mineral density (2%)
- D. Increased fluid retention (11%)
- E. Increased postprandial satiety (8%)

Omitted
Correct answer
A

73%
Answered correctly

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Time Spent

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Last Updated

Explanation

SGLT2 inhibitors

Tubule lumen | Proximal tubule cell | Interstitium

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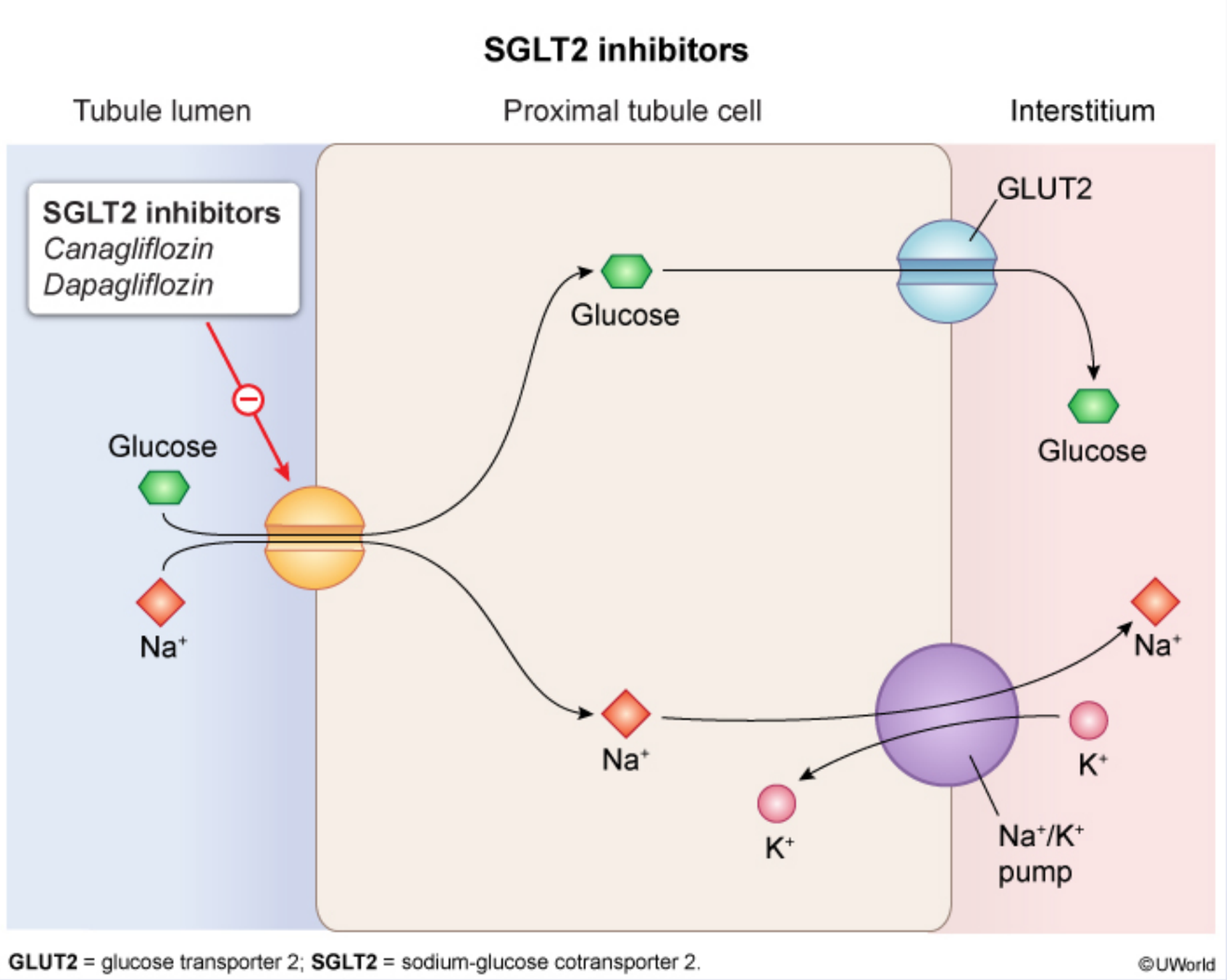

Sodium-glucose cotransporter 2 (SGLT2) is a low-affinity, high-capacity transport protein that is responsible for reabsorbing 90% of filtered glucose in the proximal renal tubule. **SGLT2 inhibitors** (eg, canagliflozin, dapagliflozin) are oral antidiabetic agents that **decrease renal reabsorption of glucose and sodium**.

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By decreasing glucose reabsorption, SGLT2 inhibitors **lower blood glucose levels**. Because the effect of SGLT2 inhibitors is dependent on the filtered glucose load, and because they do not stimulate insulin production, these medications are associated with a low risk of hypoglycemia. Patients may also experience weight loss due to glucose loss in the urine.

In addition, the decreased reabsorption of sodium and glucose induces **osmotic diuresis**, which causes a small **decrease in blood pressure**. This effect is associated with a decreased risk for cardiovascular events and a lower rate of hospitalization for heart failure. However, the resulting hypovolemia can lead to **orthostatic hypotension** in some patients and may increase the risk for acute kidney injury.

(Choice B) Due to the excess urinary glucose content, SGLT2 inhibitors are associated with an increased risk of genitourinary tract infections (eg, vaginitis, Fournier's gangrene).

(Choice C) Decreased sodium resorption can lead to increased phosphate reabsorption in the distal tubule, which can stimulate secretion of parathyroid hormone and lead to decreased bone density.

(Choice D) Thiazolidinediones (eg, pioglitazone) are antidiabetic medications that are associated with fluid retention, but the SGLT2 inhibitors induce net loss of fluid and sodium.

(Choice E) Glucagon-like polypeptide-1 (GLP-1) regulates glucose by slowing gastric emptying and increasing glucose-dependent insulin release. Pharmacologic GLP-1 agonists (eg, exenatide) are parenteral agents used for management of type 2 diabetes that increase postprandial satiety and induce weight loss.

Educational objective:
Sodium-glucose cotransporter 2 inhibitors (eg, canagliflozin, dapagliflozin) decrease renal reabsorption of glucose and sodium, leading to lower blood glucose levels. The decreased reabsorption of sodium and glucose also induces osmotic diuresis, which causes a decrease in blood pressure. Excess urinary glucose also leads to an increased risk for genitourinary tract infections.

References

- Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus

Patients may also experience weight loss due to glucose loss in the urine.

In addition, the decreased reabsorption of sodium and glucose induces **osmotic diuresis**, which causes a small **decrease in blood pressure**. This effect is associated with a decreased risk for cardiovascular events and a lower rate of hospitalization for heart failure. However, the resulting hypovolemia can lead to **orthostatic hypotension** in some patients and may increase the risk for acute kidney injury.

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References

- Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 56-year-old man comes to the office for follow-up of type 2 diabetes mellitus. The patient has had inadequate glycemic control with metformin monotherapy, and a new medication that inhibits dipeptidyl peptidase-4 was prescribed 3 months ago. He feels well and reports no adverse effects from the new therapy. The patient also has hypertension, for which he takes ramipril. He does not use tobacco, alcohol, or illicit drugs. The patient says he is generally compliant with dietary guidance but occasionally eats fast foods. Blood pressure is 126/74 mm Hg and pulse is 76/min. BMI is 31.4 kg/m^2. Physical examination shows no abnormalities. Laboratory results show a hemoglobin A1c of 6.8%. The newly prescribed medication most likely improved this patient's glycemic control through which of the following direct mechanisms?

A. Decreased dietary carbohydrate digestion

B. Decreased renal glucose reabsorption

C. Increased glucagon secretion

D. Increased glucose-dependent insulin release

E. Increased peripheral tissue glucose uptake

Submit

A 56-year-old man comes to the office for follow-up of type 2 diabetes mellitus. The patient has had inadequate glycemic control with metformin monotherapy, and a new medication that inhibits dipeptidyl peptidase-4 was prescribed 3 months ago. He feels well and reports no adverse effects from the new therapy. The patient also has hypertension, for which he takes ramipril. He does not use tobacco, alcohol, or illicit drugs. The patient says he is generally compliant with dietary guidance but occasionally eats fast foods. Blood pressure is 126/74 mm Hg and pulse is 76/min. BMI is 31.4 kg/m^2. Physical examination shows no abnormalities. Laboratory results show a hemoglobin A1c of 6.8%. The newly prescribed medication most likely improved this patient's glycemic control through which of the following direct mechanisms?

- A. Decreased dietary carbohydrate digestion (7%)
- B. Decreased renal glucose reabsorption (2%)
- C. Increased glucagon secretion (5%)
- ✓ D. Increased glucose-dependent insulin release (69%)
- E. Increased peripheral tissue glucose uptake (14%)

Omitted
Correct answer
D

69%
Answered correctly

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Explanation

GLP-1 agonists & DPP-4 inhibitors

Nutrients

GLP-1 agonists:
• Exenatide

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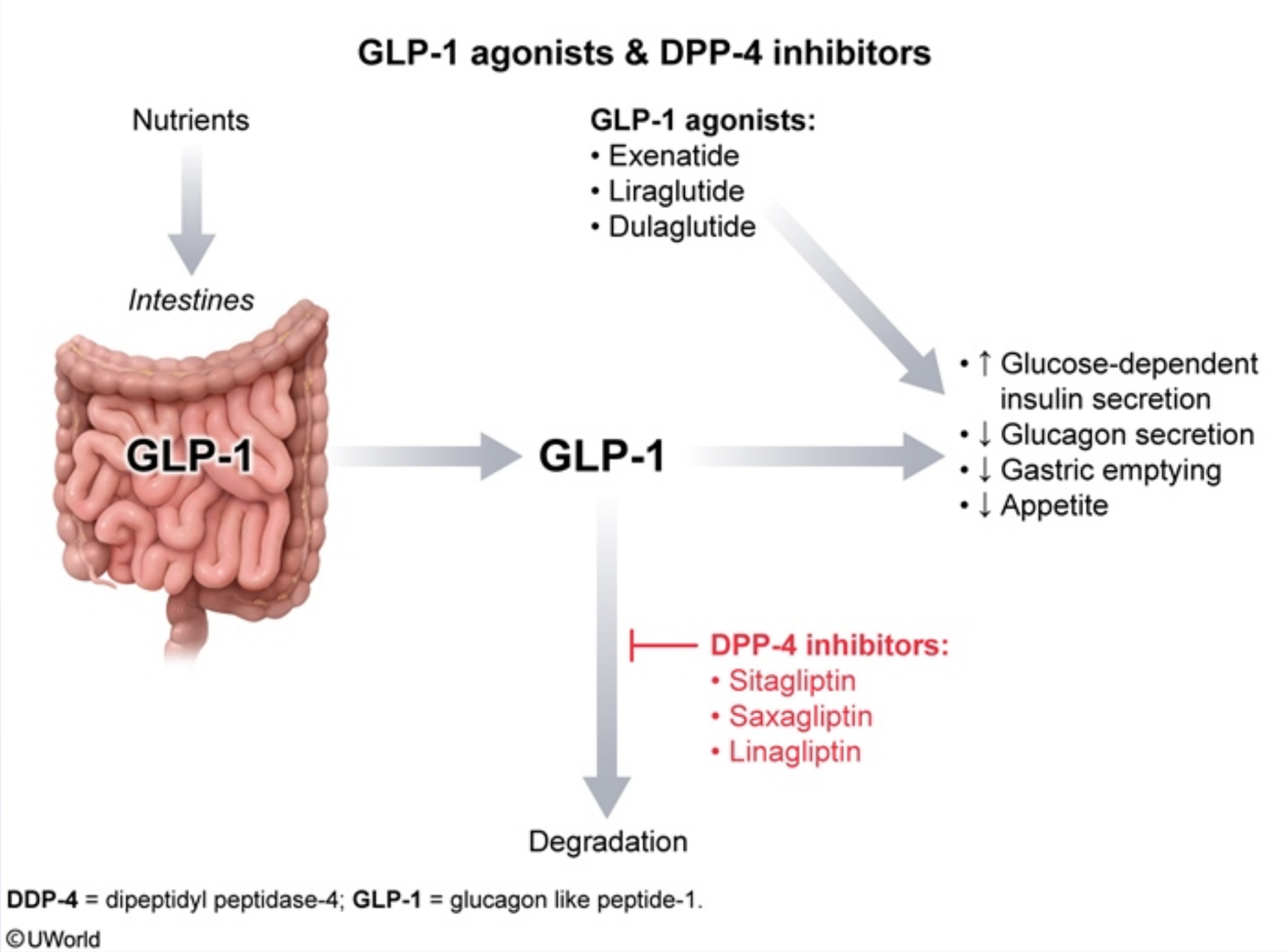

Glucagon-like peptide-1 (GLP-1) is secreted by intestinal L cells in response to food intake and regulates glucose levels by slowing gastric emptying, suppressing glucagon secretion, and **increasing glucose-dependent insulin release**. It acts through cell surface receptors that are coupled with a G protein–adenylyl cyclase system. Native GLP-1 is degraded by dipeptidyl peptidase-4 (DPP-4).

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DPP-4 inhibitors (eg, sitagliptin, saxagliptin) **inhibit the degradation of GLP-1**, prolonging its effects and leading to improved glycemic control (eg, reduction in hemoglobin A1c). GLP-1's effect on insulin secretion is glucose-dependent: as glucose levels fall, so does insulin secretion. Therefore, DPP-4 inhibitors have a **low risk of hypoglycemia**. Major side effects include nasopharyngitis and other upper respiratory symptoms.

GLP-1 agonists that are intrinsically resistant to degradation by DPP-4 are also available and have a similar (but more potent) effect in lowering blood glucose with a low risk of hypoglycemia.

(Choice A) Alpha-glucosidase inhibitors (eg, acarbose) directly impair the hydrolysis of polymeric carbohydrates, leading to decreased postprandial glucose absorption. Although DPP-4 inhibitors can indirectly slow digestion of carbohydrates due to delayed gastric emptying, they do not directly affect intestinal carbohydrate metabolism.

(Choice B) Sodium-glucose cotransporter-2 inhibitors (eg, canagliflozin, dapagliflozin) act in the kidney to decrease reabsorption of filtered glucose.

(Choice C) GLP-1 acts directly on pancreatic islet cells to suppress glucagon secretion, an effect that is enhanced by DPP-4 inhibitors.

(Choice E) Metformin inhibits the mitochondrial enzymes required for gluconeogenesis, leading to decreased hepatic glucose production and lower circulating glucose levels. It also increases peripheral glucose uptake and improves insulin sensitivity by activating AMP-activated protein kinase.

Educational objective:
Glucagon-like peptide-1 (GLP-1) regulates glucose by slowing gastric emptying, suppressing glucagon secretion, and increasing glucose-dependent insulin release. Dipeptidyl peptidase-4 inhibitors (eg, sitagliptin, saxagliptin) decrease the breakdown of GLP-1 and improve glycemic control in patients with type 2 diabetes. Because the effect on insulin is glucose-dependent, these medications have a low risk of hypoglycemia.

References

- Clinical pharmacology of dipeptidyl peptidase 4 inhibitors indicated for the treatment of type 2 diabetes mellitus.

(eg, reduction in hemoglobin A1c). GLP-1's effect on insulin secretion is glucose-dependent: as glucose levels fall, so does insulin secretion. Therefore, DPP-4 inhibitors have a **low risk of hypoglycemia**. Major side effects include nasopharyngitis and other upper respiratory symptoms.

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References

- Clinical pharmacology of dipeptidyl peptidase 4 inhibitors indicated for the treatment of type 2 diabetes mellitus.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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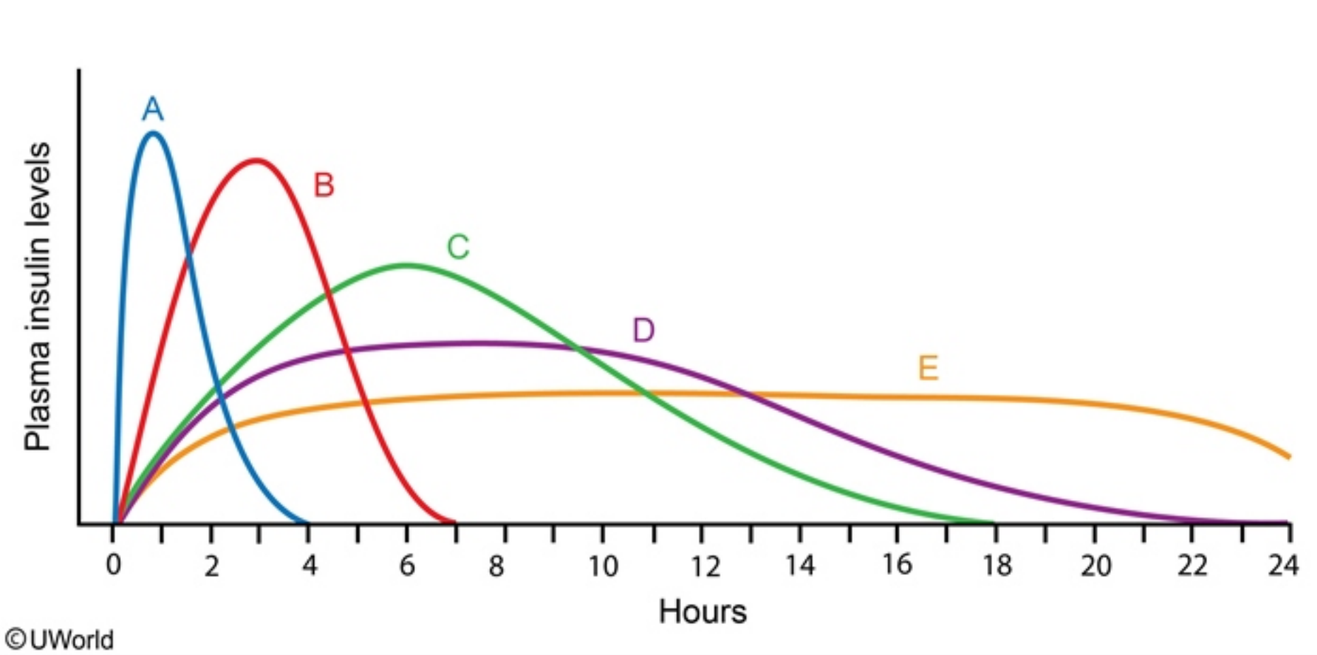
A 21-year-old man comes to the emergency department due to several days of dizziness and extreme fatigue. The patient has been drinking a lot of water and urinating more than usual for the past 2 weeks. He developed nausea and vomiting a day ago and has had difficulty keeping food and liquids down since then. The patient has no other medical conditions and takes no medications. Blood pressure is 90/60 mm Hg, pulse is 120/min, and respirations are 20/min. Urinalysis is positive for glucose and ketones. The patient is given intravenous fluids and an intravenous infusion of recombinant human insulin without any amino acid modification. After his condition is stabilized, the insulin infusion is stopped, and the same insulin formulation is administered subcutaneously. Which of the following drug concentration curves is most likely to be obtained after the subcutaneous insulin injection?



A. A
B. B
C. C

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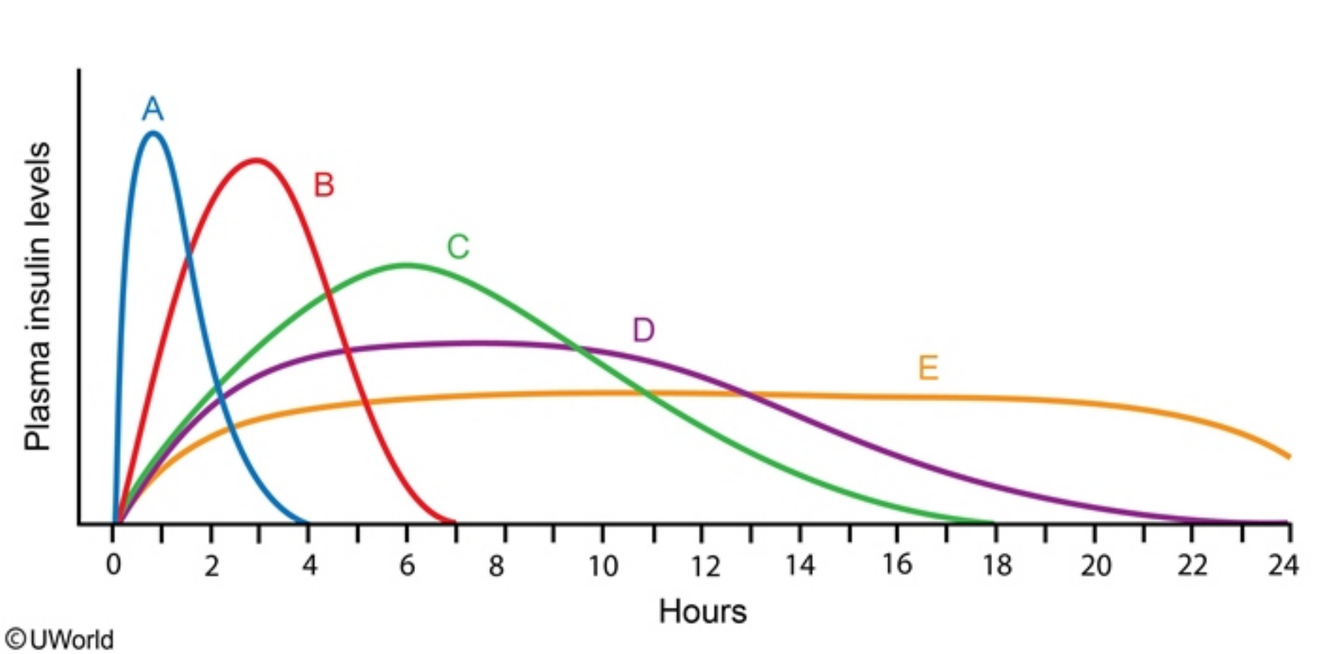

A. A (9%)
✓ B. B (50%)
C. C (24%)
D. D (8%)
E. E (8%)

Omitted
Correct answer

50%
Answered correctly

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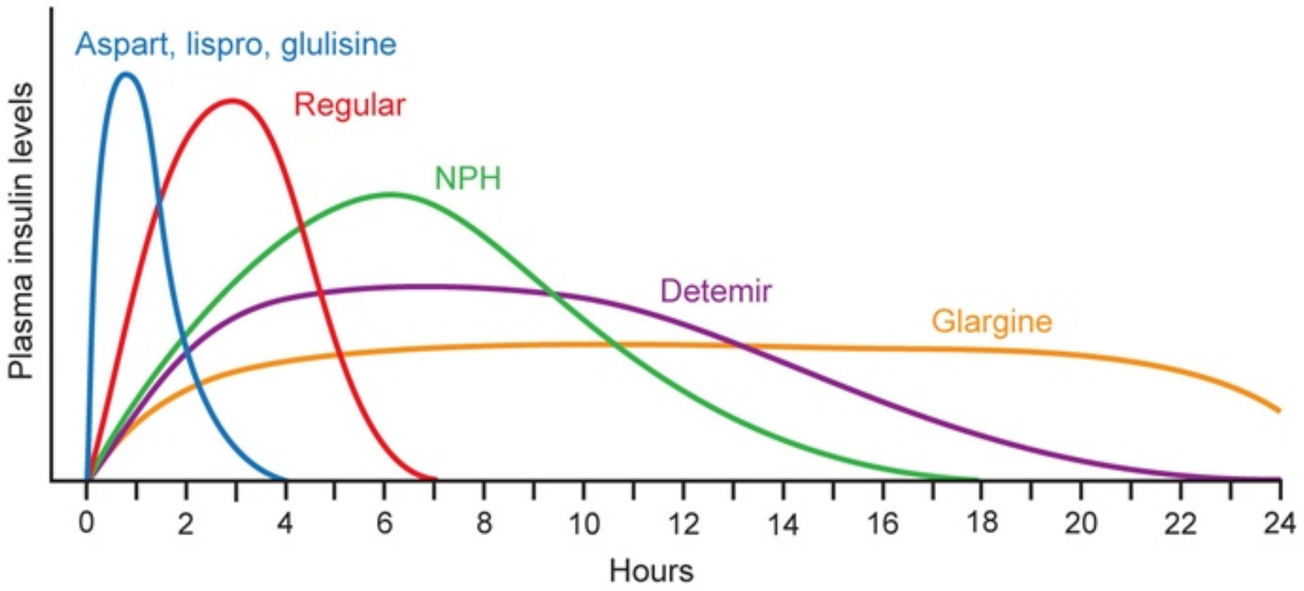
Pharmacokinetic profiles of common insulin preparations



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This patient's vomiting, volume depletion, glucosuria, and ketonuria are consistent with **diabetic ketoacidosis** (DKA). DKA is treated with an intravenous infusion of **regular insulin** that begins to lower serum glucose and ketone levels within minutes of administration. Regular insulin has a half-life of 5 minutes when administered **intravenously**, allowing rapid adjustment of the infusion rate based on glucose levels.

Regular insulin can also be used subcutaneously in the subacute and chronic management of diabetes, usually in combination with an intermediate-acting or a long-acting insulin analog to provide bolus and basal coverage. When given **subcutaneously**, regular insulin can polymerize into hexamers, which slightly delays systemic absorption; it starts working within 30 minutes, **peaks in 2-4 hours**, and lasts 5-8 hours.

Regular insulin and neutral protamine Hagedorn (NPH) are the only human recombinant insulins without any modifications in the amino acid sequence. All other insulin preparations (eg, detemir, glargine, lispro, aspart, glulisine) have structural modifications (eg, amino acid modifications) and are considered **insulin analogs**.

(Choice A) Insulin lispro, aspart, and glulisine are rapid-acting insulin analogs. Due to various amino acid modifications, they do not form

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(Choice A) Insulin lispro, aspart, and glulisine are rapid-acting insulin analogs. Due to various amino acid modifications, they do not form hexamers like regular insulin, and are absorbed more quickly after subcutaneous injection. They have an onset of action of about 15 minutes and peak in 45-75 minutes.

(Choice C) NPH insulin is an intermediate-acting insulin composed of a crystalline suspension of insulin with protamine and zinc. This delays absorption of insulin from the subcutaneous injection site. NPH usually starts working within 2 hours, peaks in 4-12 hours, and lasts about 18 hours.

(Choice D) Detemir is a long-acting insulin analog with a fatty acid bound to one of the lysine amino acids on the insulin molecule. This fatty acid side chain allows detemir to bind to albumin and slowly dissociate, resulting in prolonged action. It usually starts working within 2 hours, peaks between 3-9 hours, and lasts up to 24 hours.

(Choice E) Glargine is an insulin analog with a long duration of action. Glargine has a pH of 4 and forms a microprecipitate in the subcutaneous tissue after injection, resulting in a very slow release of insulin. Glargine lasts about 24 hours and does not have a pronounced peak. Longer-acting basal insulin analogs (eg, insulin degludec and concentrated glargine) with duration of action >24 hours are also available.

Educational objective:
Diabetic ketoacidosis is initially treated with an intravenous infusion of regular insulin, which allows for rapid adjustments in dose based on blood glucose levels. When given subcutaneously, regular insulin starts working within 30 minutes, peaks in 2-4 hours, and lasts 5-8 hours.

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Diabetic ketoacidosis is initially treated with an intravenous infusion of regular insulin, which allows for rapid adjustments in dose based on blood glucose levels. When given subcutaneously, regular insulin starts working within 30 minutes, peaks in 2-4 hours, and lasts 5-8 hours.

References

- New insulin preparations: a primer for the clinician.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 63-year-old man comes to the office for a follow-up visit. Two months ago, he was hospitalized for chest pain and was found to have a blockage in the left anterior descending artery. He had percutaneous coronary intervention with placement of a drug-eluting stent, and was discharged on appropriate medical therapy. His other medical problems include hypertension, type 2 diabetes mellitus, and degenerative joint disease. The patient has been taking all his medications as prescribed. He has no chest pain but does have diffuse muscle aches and cramps, especially after exercise. Physical examination is unremarkable. Laboratory testing reveals elevated serum creatine kinase. The medication most likely responsible for this patient's current findings also causes which of the following effects?

A. Decreased gastric mucosal prostaglandin synthesis

B. Elevated plasma bradykinin level

C. Impaired potassium entry into cells

D. Increased hepatocyte LDL receptor recycling

E. Increased renal calcium reabsorption

F. Inhibition of hepatic gluconeogenesis

Submit

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- A. Decreased gastric mucosal prostaglandin synthesis (3%)
- B. Elevated plasma bradykinin level (6%)
- C. Impaired potassium entry into cells (7%)
- ✓ D. Increased hepatocyte LDL receptor recycling (64%)
- E. Increased renal calcium reabsorption (4%)
- F. Inhibition of hepatic gluconeogenesis (13%)

Omitted
Correct answer
D

64%
Answered correctly

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Time Spent

01/19/2020
Last Updated

Explanation

This patient's symptoms are most likely due to **statin-induced myopathy**. Statins are an effective treatment for hypercholesteremia and are now routinely prescribed for all patients with symptomatic coronary artery disease, regardless of baseline cholesterol levels. Myopathy is the most common complication of statin use, and symptoms can range from myalgia or myopathy, with or without myonecrosis (elevated serum creatine

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Statins act through competitive **inhibition** of **HMG-CoA reductase**, preventing conversion of HMG-CoA to mevalonic acid (the rate-limiting step in cholesterol biosynthesis). Decreased liver cholesterol synthesis leads to increased hepatic clearance of LDL from the circulation by LDL receptors. After mediating endocytosis of LDL particles, the LDL receptors are returned to the cell surface for reuse (receptor recycling); LDL is digested and used for metabolic purposes. This **increase in LDL receptor recycling** allows intrahepatic cholesterol levels to remain at normal levels while blood levels are kept low.

(Choice A) Nonsteroidal anti-inflammatory drugs inhibit cyclooxygenase (prostaglandin synthase), leading to decreased synthesis of gastric mucosal prostaglandin.

(Choice B) Angiotensin-converting enzyme (ACE) inhibitors inhibit the conversion of angiotensin I to angiotensin II. ACE also acts as a kininase, and ACE inhibition also leads to increased plasma bradykinin levels.

(Choice C) Stimulation of beta-2 receptors by catecholamines increases extracellular potassium movement into cells. This effect is blocked by beta-blockers (primarily non-selective agents such as propranolol or labetalol), which impair potassium entry into cells and cause minor elevations in plasma potassium.

(Choice E) Thiazide diuretics increase calcium reabsorption in the distal tubule of the nephron and can lead to hypercalcemia. In contrast, decreased calcium excretion is useful in patients with renal stones due to hypercalciuria.

(Choice F) Metformin inhibits hepatic gluconeogenesis via inhibition of the mitochondrial isoform of glycerophosphate dehydrogenase in the liver. Typical side effects of metformin include gastrointestinal upset and diarrhea. Myopathy is not a common effect.

Educational objective:
Statins inhibit the intracellular rate-limiting step of cholesterol biosynthesis via competitive inhibition of HMG-CoA reductase. This leads to enhanced hepatic LDL receptor recycling and increased LDL clearance from the circulation. Statin-induced myopathy (eg, myalgia, elevated creatine kinase) is the most common complication of statin use.

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Educational objective:
Statins inhibit the intracellular rate-limiting step of cholesterol biosynthesis via competitive inhibition of HMG-CoA reductase. This leads to enhanced hepatic LDL receptor recycling and increased LDL clearance from the circulation. Statin-induced myopathy (eg, myalgia, elevated creatine kinase) is the most common complication of statin use.

References

- Inhibitors of cholesterol biosynthesis increase hepatic low-density lipoprotein receptor protein degradation.
- The LDL receptor.

Pharmacology	Endocrine, Diabetes & Metabolism	Drug induced myopathy
Subject	System	Topic

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A 56-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. She is managing her condition with a healthy diet and regular exercise and is on the maximum tolerated dose of metformin. Despite this, the patient's diabetes has been inadequately controlled for the last 6 months, with an average fasting glucose level of 170 mg/dL and a hemoglobin A1c of 8.0%. She has no known diabetes-related complications. Medical history includes hypertension, for which she takes lisinopril and amlodipine. After discussing various medication options, it is decided to add pioglitazone to her current regime. Before starting this medication, this patient should be educated about which of the following adverse drug effects?

A. Agranulocytosis
B. Hepatic injury
C. Hypoglycemia
D. Lactic acidosis
E. Orthostatic hypotension
F. Weight gain and edema

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- A. Agranulocytosis (2%)
- B. Hepatic injury (5%)
- C. Hypoglycemia (12%)
- D. Lactic acidosis (2%)
- E. Orthostatic hypotension (2%)
- ✓ F. Weight gain and edema (75%)

Omitted
Correct answer
F

75%
Answered correctly

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Explanation

Thiazolidinedione mechanism of action

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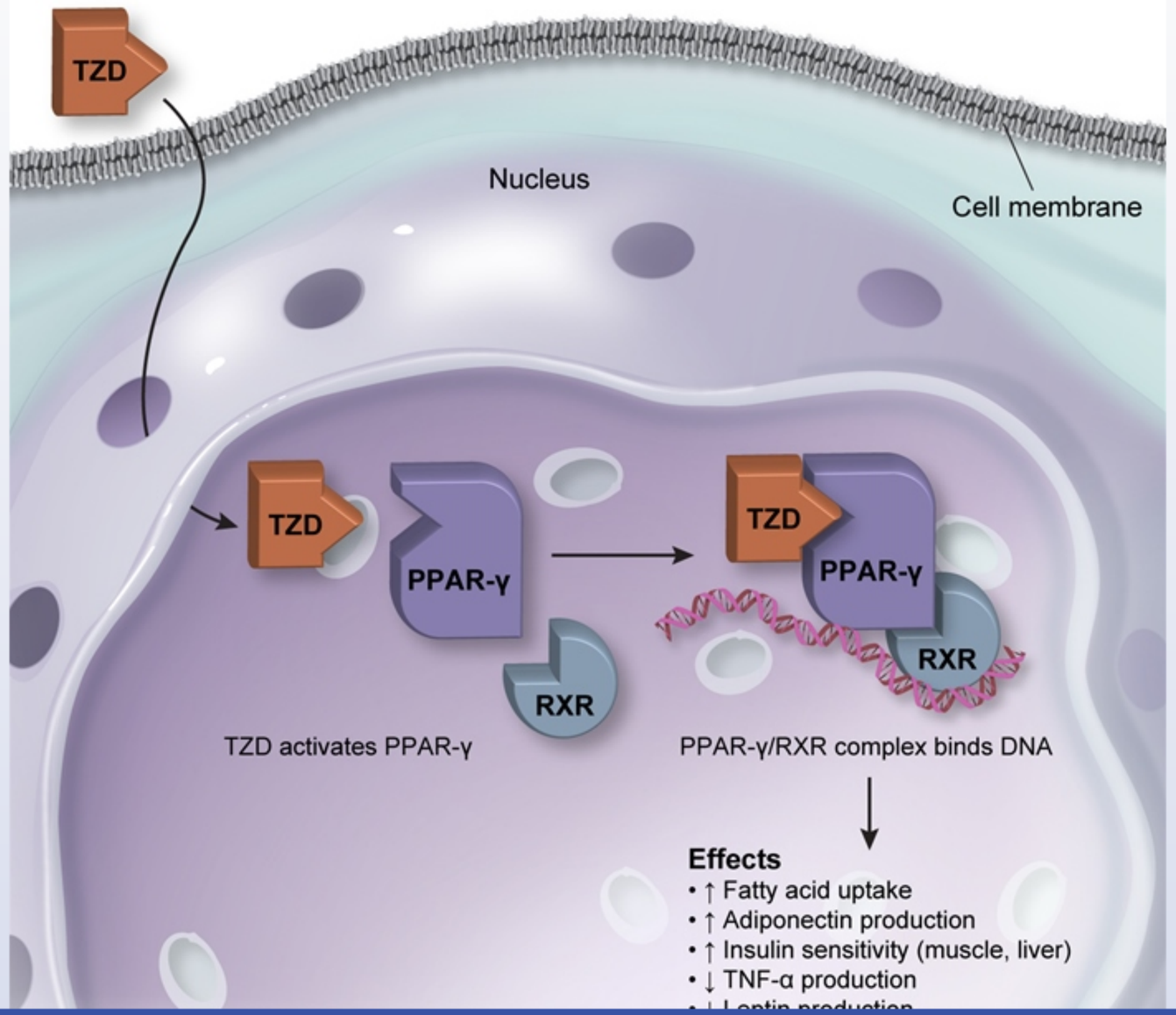
Thiazolidinedione mechanism of action



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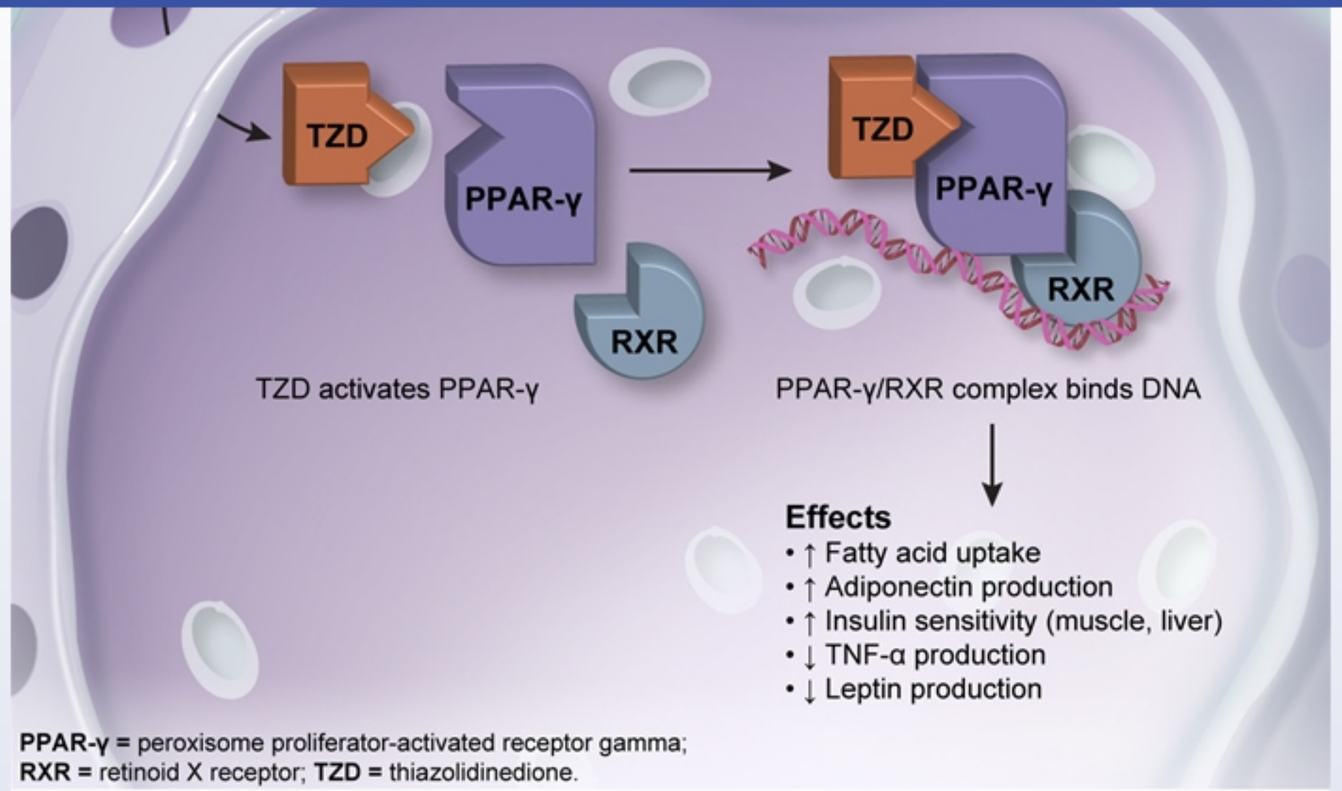

PPAR-γ = peroxisome proliferator-activated receptor gamma; **RXR** = retinoid X receptor; **TZD** = thiazolidinedione.

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Thiazolidinediones (TZDs) (eg, pioglitazone) activate peroxisome proliferator-activated receptor gamma, a transcriptional regulator that affects expression of genes involved in glucose and lipid metabolism. TZDs cause reduced insulin resistance and a decrease in blood glucose levels. Because their effect requires an alteration in gene transcription and protein synthesis, maximal glucose lowering may take place days to weeks after initiating therapy.

The main side effect of TZDs is **fluid retention** due to increased sodium reabsorption in the renal collecting tubules and increased vascular permeability in adipose tissue. This can cause water weight gain, peripheral edema, and decompensation of underlying **congestive heart failure**. Fluid retention is often worse when TZDs are given with insulin. TZDs also cause **adipose weight gain**, likely due to increased fat storage in adipocytes and an increased number of adipocytes in subcutaneous tissue.

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(Choice A) Agranulocytosis is seen with certain antithyroid medications (eg, methimazole) and is a rare complication of sulfonylurea therapy. It is not seen with TZDs.

(Choice B) Hepatic toxicity was seen with an older TZD, troglitazone, which is no longer available. The current TZDs (pioglitazone and rosiglitazone) do not cause significant hepatotoxicity.

(Choice C) TZDs increase insulin sensitivity rather than insulin secretion. As a result, they have a low risk of hypoglycemia, although they can increase the risk if used in combination with insulin or sulfonylureas.

(Choice D) Lactic acidosis is a potential side effect of metformin, although it is rare when used in patients with normal renal, hepatic, and cardiac function.

(Choice E) Sodium-glucose cotransporter 2 inhibitors (eg, canagliflozin) can induce osmotic diuresis, leading to volume depletion and orthostatic hypotension. TZDs do not commonly cause orthostatic hypotension.

Educational objective:
Thiazolidinediones (eg, pioglitazone) can cause fluid retention, leading to peripheral edema and weight gain. The excess fluid can potentially exacerbate underlying congestive heart failure.

References

- Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials.

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A 34-year-old man comes to the office with his girlfriend for follow-up of type 1 diabetes mellitus. He was diagnosed 15 years ago and is currently treated with a combination of basal and rapid-acting insulin injections. The patient has been experiencing intermittent episodes of hypoglycemia with a blood glucose of 35-54 mg/dL. Two weeks ago, he was taken to the emergency department after passing out due to low glucose levels. The patient is prescribed an injectable medication to be administered at home by a caregiver when hypoglycemia is associated with impaired consciousness. This medication rapidly improves hypoglycemia by which of the following mechanisms?

A. Decreasing uptake of glucose by fat and muscles

B. Decreasing uptake of glucose by the liver

C. Increasing gastrointestinal absorption of glucose

D. Increasing gluconeogenesis

E. Increasing glycogenolysis

Submit

A 34-year-old man comes to the office with his girlfriend for follow-up of type 1 diabetes mellitus. He was diagnosed 15 years ago and is currently treated with a combination of basal and rapid-acting insulin injections. The patient has been experiencing intermittent episodes of hypoglycemia with a blood glucose of 35-54 mg/dL. Two weeks ago, he was taken to the emergency department after passing out due to low glucose levels. The patient is prescribed an injectable medication to be administered at home by a caregiver when hypoglycemia is associated with impaired consciousness. This medication rapidly improves hypoglycemia by which of the following mechanisms?

A. Decreasing uptake of glucose by fat and muscles (10%)

B. Decreasing uptake of glucose by the liver (6%)

C. Increasing gastrointestinal absorption of glucose (3%)

D. Increasing gluconeogenesis (34%)

✓ E. Increasing glycogenolysis (46%)

Omitted
Correct answer
E

46%
Answered correctly

02 secs
Time Spent

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Last Updated

Explanation

Metabolic effects of glucagon	
Liver	• ↑ glycogenolysis (primary) • ↑ gluconeogenesis, ↓ glycolysis (secondary) • ↓ lipogenesis

Metabolic effects of glucagon	
Liver	• ↑ glycogenolysis (primary) • ↑ gluconeogenesis, ↓ glycolysis (secondary) • ↓ lipogenesis
Adipose	• ↑ lipolysis
Heart	• ↑ heart rate, contractility (high dose) • Useful in treating beta blocker overdose

Hypoglycemia initially manifests with neurogenic (autonomic) symptoms, including anxiety, tremor, and sweating. However, as hypoglycemia worsens patients may develop life-threatening neuroglycopenic symptoms, including confusion, **loss of consciousness**, and seizures. Mild to moderate hypoglycemia is usually self-treated with oral fast-acting carbohydrates (eg, glucose tablets, fruit juices). However, when hypoglycemia becomes severe enough to induce unconsciousness, **parenteral treatment** is necessary.

In a medical setting, severe hypoglycemia is usually treated with an infusion of glucose, but this requires intravenous access. In a nonmedical setting, severe hypoglycemia can be treated with **emergency glucagon kits**, which are produced in intranasal and subcutaneous/intramuscular formulations and can be administered by a caregiver or informed bystander.

Glucagon rapidly corrects hypoglycemia by **increasing hepatic glycogenolysis**; the free glucose residues are then released into the blood, causing a return to consciousness within 10-15 minutes of administration. Subsequently, glucagon induces gluconeogenesis and suppresses hepatic glucose uptake, which provide a delayed but somewhat more sustained effect **(Choices B and D)**.

(Choice A) Glucagon has little direct effect on glucose uptake in adipose and muscle tissue, which is primarily regulated by insulin. Although epinephrine raises blood glucose (in part) by suppression of peripheral glucose uptake and can be administered by auto-injector, it is less effective than glucagon for hypoglycemia and is primarily used for severe allergy/anaphylaxis.

(Choice C) Glucose is taken up from the intestinal lumen into epithelial cells via sodium-glucose cotransporter-1 (SGLT-1) and then passed into the blood via glucose transporter 2 (GLUT-2). Glucagon causes a decrease in intestinal motility but does not have a major effect on the transport of glucose by SGLT-1 or GLUT-2.

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Educational objective:
Severe hypoglycemia causing impaired conciousness can be treated by a caregiver or bystander with injectable or intranasal glucagon. Glucagon rapidly corrects hypoglycemia by increasing hepatic glycogenolysis, resulting in the release of glucose from preexisting hepatic glycogen stores.

References

- Novel preparations of glucagon for the prevention and treatment of hypoglycemia.

Pharmacology	Endocrine, Diabetes & Metabolism	Hypoglycemia
Subject	System	Topic

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A 68-year-old man reports myalgia and fatigue during a follow-up office visit. The patient has been taking high-intensity statin therapy since he had an acute myocardial infarction several weeks ago. His other medical problems include hypertension and type 2 diabetes mellitus. On examination, there is mild generalized muscle tenderness. Serum creatine kinase level is 456 U/L. Vitamin D and TSH levels are within normal range. The patient's statin therapy is discontinued, and he is started on a medication that inhibits cholesterol absorption at the brush border of the small intestine. Which of the following drugs was most likely started in this patient?

A. Colesevelam

B. Ezetimibe

C. Fenofibrate

D. Nicotinic acid

E. PCSK9 inhibitor

Submit

A 68-year-old man reports myalgia and fatigue during a follow-up office visit. The patient has been taking high-intensity statin therapy since he had an acute myocardial infarction several weeks ago. His other medical problems include hypertension and type 2 diabetes mellitus. On examination, there is mild generalized muscle tenderness. Serum creatine kinase level is 456 U/L. Vitamin D and TSH levels are within normal range. The patient's statin therapy is discontinued, and he is started on a medication that inhibits cholesterol absorption at the brush border of the small intestine. Which of the following drugs was most likely started in this patient?

- A. Colesevelam (9%)
- ✓ B. Ezetimibe (77%)
- C. Fenofibrate (10%)
- D. Nicotinic acid (1%)
- E. PCSK9 inhibitor (2%)

Omitted
Correct answer
B

77%
Answered correctly

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Explanation

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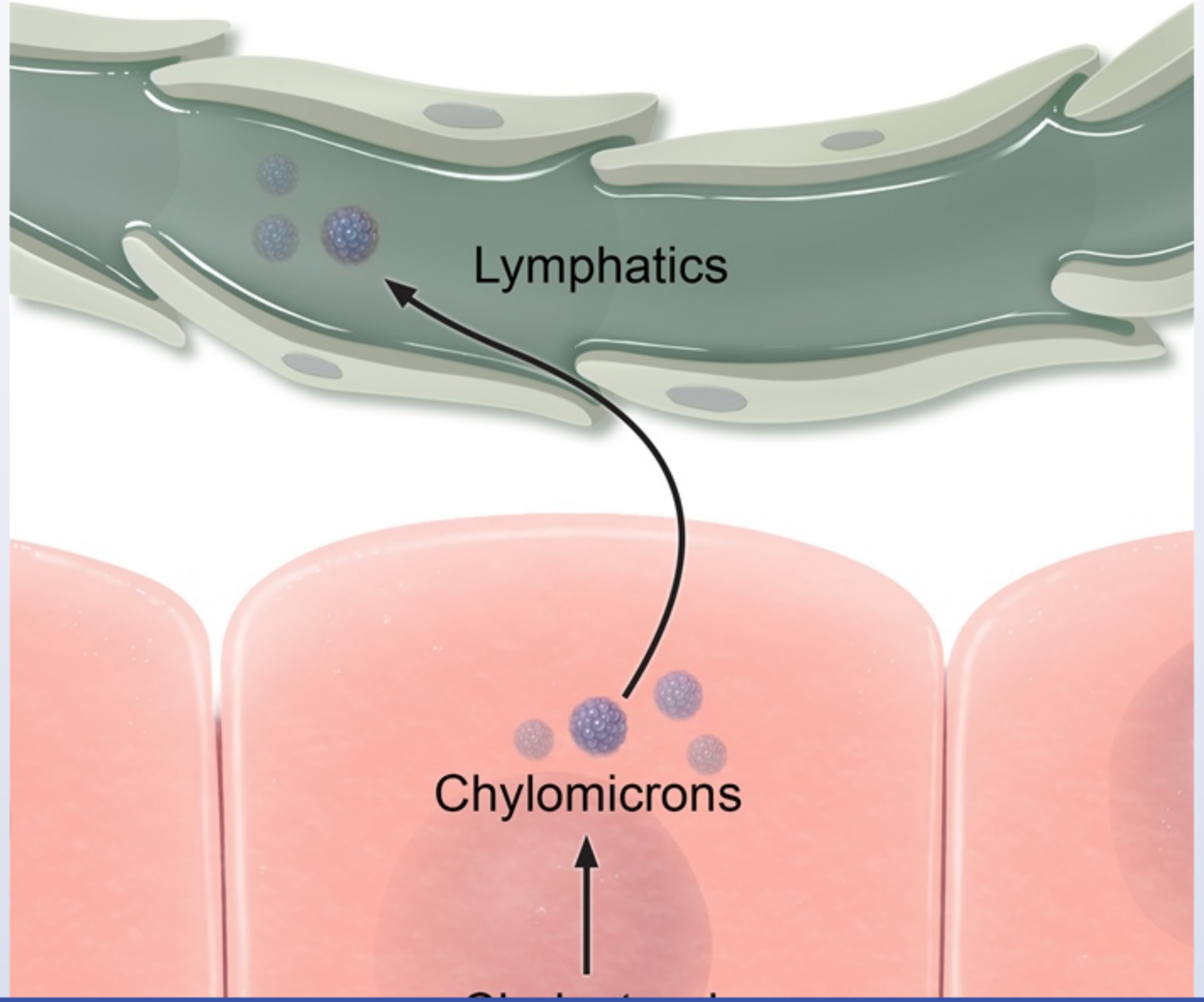
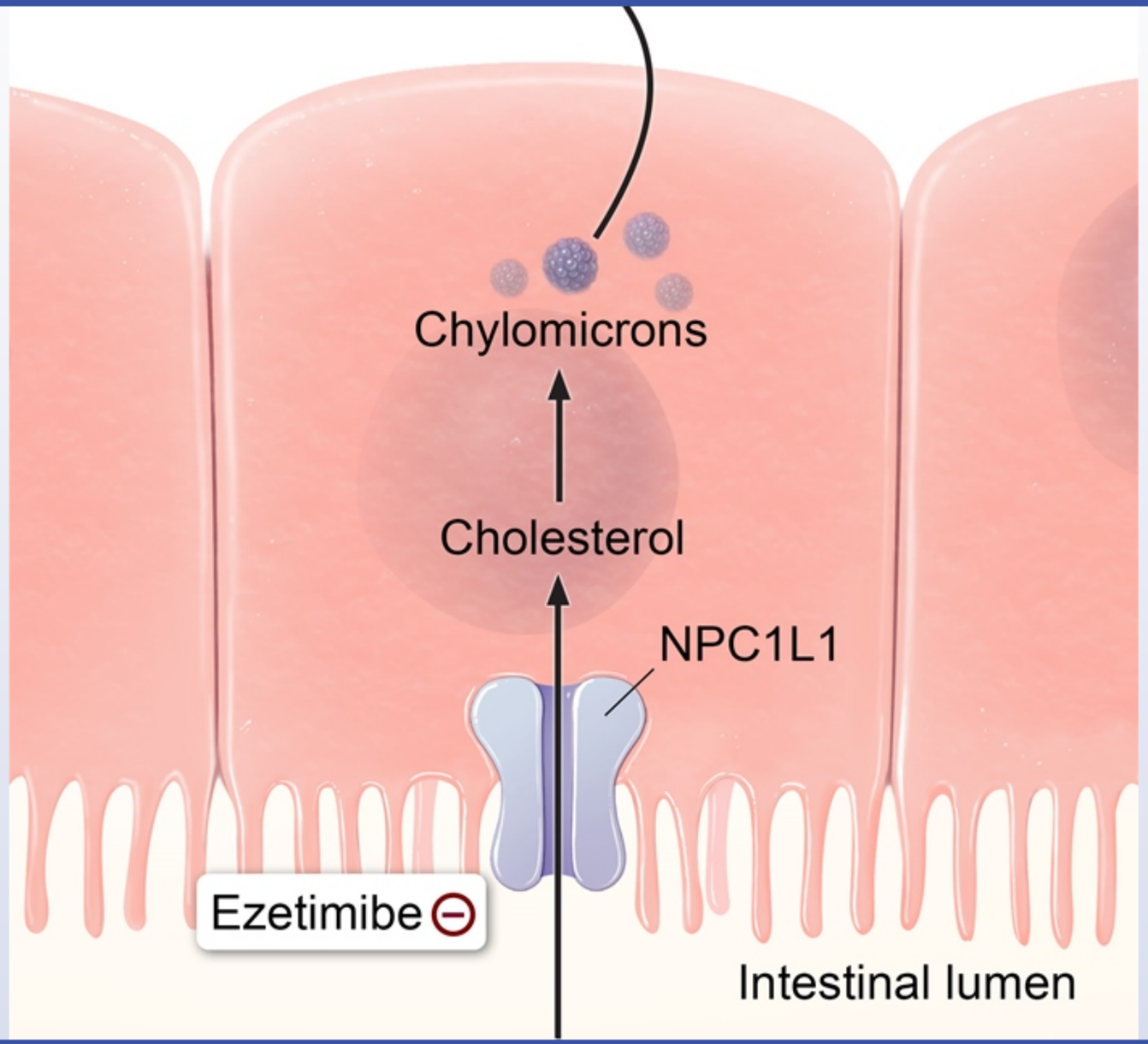
Ezetimibe mechanism of action




Chylomicrons
Cholesterol
NPC1L1
Ezetimibe
Intestinal lumen

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Cholesterol-lowering agents commonly work in 1 of 3 ways:

- Decreasing hepatic cholesterol synthesis
- Decreasing intestinal cholesterol absorption
- Altering cholesterol transport between the blood and tissues

Ezetimibe decreases **intestinal absorption** of cholesterol by inhibiting the Niemann-Pick C1-like 1 (NPC1L1) transporter protein, which transports dietary cholesterol from the gastrointestinal lumen into intestinal enterocytes. As a result, the total amount of dietary cholesterol reaching the liver decreases, lowering intrahepatocyte cholesterol levels. To compensate, the liver increases LDL receptor expression, which draws cholesterol out of the circulation.

(Choice A) Bile acid sequestrants (eg, colesevelam) bind bile salts in the intestine, decreasing their reabsorption. Subsequent depletion of the bile acid pool causes upregulation of cholesterol 7-α-hydroxylase, which converts cholesterol into bile acids.

(Choice C) Fibrates activate peroxisome proliferator-activated receptor-alpha transcription factors, which leads to stimulation of lipoprotein lipase activity and a decrease in triglyceride levels.

(Choice D) Nicotinic acid inhibits hepatic triglyceride synthesis, which in turn reduces the liver's availability to synthesize VLDL particles that are subsequently metabolized into LDL in the circulation.

(Choice E) Proprotein convertase subtilisin kexin 9 (PCSK9) increases degradation of hepatic LDL receptors. Alirocumab is a monoclonal antibody against PCSK9 that blocks this effect, resulting in increased availability of LDL receptors on hepatocyte membranes and subsequently increased clearance of LDL from the blood.

Educational objective:
Ezetimibe reduces intestinal absorption of cholesterol. As a result, the amount of dietary cholesterol reaching the liver decreases. To compensate, the liver increases LDL receptor expression, which draws cholesterol out of the circulation.

References

- Ezetimibe--a new approach in hypercholesterolemia management.
- Inactivating mutations in NPC1L1 and protection from coronary heart disease.

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Cholesterol-lowering agents commonly work in 1 of 3 ways:

- Decreasing hepatic
- Decreasing intestina
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(Choice E) Proprotein co
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Educational objective:
Ezetimibe reduces intestin
compensate, the liver incr

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- Inactivating mutations in NPC1L1 and protection from coronary heart disease.

Exhibit Display

Antihyperlipidemic medications

Drug	Mechanism	Major lipid effects	Side effects
Statins	• Inhibit HMG-CoA reductase	• ↓↓ **LDL** • ↓ Triglycerides	• Hepatotoxicity • Muscle toxicity
Ezetimibe	• ↓ Intestinal cholesterol absorption	• ↓ LDL	• ↑ Hepatotoxicity if given with statins
Bile acid sequestrants	• Prevent reabsorption of bile acids in the intestine	• ↓ LDL	• Nausea, bloating, cramping • Impaired absorption of drug & fat-soluble vitamin
Niacin	• ↓ Fatty acid release • ↓ VLDL synthesis • ↓ HDL clearance	• ↓ LDL • ↑↑ HDL	• Flushing & pruritus • Hepatotoxicity • Hyperuricemia/gout
Fibrates	• Activate PPAR-α • ↓ VLDL synthesis	• ↓↓ **Triglycerides** • ↑ HDL	• Muscle toxicity • Gallstones
Fish oil/omega-3 fatty	• ↓ VLDL synthesis • ↓ Apolipoprotein B	• ↓ Triglycerides	• Fishy taste

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Cholesterol-lowering agents commonly work in 1 of 3 ways:

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Exhibit Display

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Niacin	• ↓ Fatty acid release • ↓ VLDL synthesis • ↓ HDL clearance	• ↓ LDL • ↑↑ HDL	• Flushing & pruritus • Hepatotoxicity • Hyperuricemia/gout
Fibrates	• Activate PPAR-α • ↓ VLDL synthesis	• ↓↓ **Triglycerides** • ↑ HDL	• Muscle toxicity • Gallstones
Fish oil/omega-3 fatty acids	• ↓ VLDL synthesis • ↓ Apolipoprotein B synthesis	• ↓ Triglycerides • ↑ HDL	• Fishy taste

PPAR-α = peroxisome proliferator-activated receptor-alpha.

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A 32-year-old previously healthy woman comes to the office due to several weeks of anxiety, palpitations, excessive sweating, and thinning hair. The symptoms have progressively worsened and interfered significantly with her daily activities. The patient does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/70 mm Hg and pulse is 104/min. On physical examination, there is lid lag, moderate exophthalmos, and fine tremors of the outstretched hands. After the diagnosis is made, she is prescribed propranolol for immediate symptom control. Which of the following findings is most likely to persist in this patient despite this therapy?

A. Anxiety
B. Diaphoresis
C. Exophthalmos
D. Hand tremor
E. Heat intolerance
F. Palpitations

Submit

A 32-year-old previously healthy woman comes to the office due to several weeks of anxiety, palpitations, excessive sweating, and thinning hair. The symptoms have progressively worsened and interfered significantly with her daily activities. The patient does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/70 mm Hg and pulse is 104/min. On physical examination, there is lid lag, moderate exophthalmos, and fine tremors of the outstretched hands. After the diagnosis is made, she is prescribed propranolol for immediate symptom control. Which of the following findings is most likely to persist in this patient despite this therapy?

A. Anxiety (3%)
B. Diaphoresis (6%)
✓ C. Exophthalmos (84%)
D. Hand tremor (2%)
E. Heat intolerance (2%)
F. Palpitations (0%)

Omitted
Correct answer
C

84%
Answered correctly

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04/25/2020
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Explanation

General manifestations of hyperthyroidism	
	• Anxiety & insomnia • Palpitations

General manifestations of hyperthyroidism	
Symptoms	• Anxiety & insomnia • Palpitations • Heat intolerance • Increased perspiration • Weight loss without decreased appetite
Physical examination	• Goiter • Hypertension • Tremors involving fingers/hands • Hyperreflexia • Proximal muscle weakness • Lid lag • Atrial fibrillation

Graves disease is an autoimmune disorder characterized by autoantibodies that bind to and activate the TSH receptor (**thyrotropin receptor antibodies** [TRAb]). In the thyroid, TRAb triggers release of thyroid hormones, leading to thyrotoxicosis. Hyperthyroidism causes increased expression of **beta-adrenergic receptors** in various organs, and the subsequent hyperadrenergic state can result in hypertension, tremor, heat intolerance, palpitations/tachycardia, and hyperreflexia **(Choices D, E, and F)**. Patients with Graves disease are frequently given beta-adrenergic blocking medications (eg, propranolol) to control these manifestations while awaiting definitive management.

TSH receptors are also present on fibroblasts, adipocytes, and other tissues. Graves ophthalmopathy results from stimulation of orbital fibroblasts and adipocytes by TRAb and activated T cells. The fibroblasts secrete excess amounts of glycosaminoglycans, leading to expansion of the ground substance of retro-orbital tissues. This, along with excess adipose deposition, displaces the globe forward (**exophthalmos**) and leads to restricted movement of the extraocular muscles (eg, diplopia). These manifestations are not mediated by thyroid hormone or adrenergic stimulation and do not respond to beta blockers. However, as they are **immune mediated**, the manifestations of Graves ophthalmopathy usually respond to **glucocorticoid therapy**.

(Choice A) Although beta blockers can cause fatigue and depressive symptoms, they help reduce fatigue and mood lability in patients with

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(Choice A) Although beta blockers can cause fatigue and depressive symptoms, they help reduce fatigue and mood lability in patients with Graves disease by ameliorating sympathetic overactivation. Beta blockers can also help blunt the physical manifestations of anxiety.

(Choice B) Apocrine sweat glands are stimulated primarily by catecholamines; beta blockers can reduce secretory activity. By contrast, eccrine sweat glands are directly innervated by cholinergic fibers. However, centrally acting beta blockers (eg, propranolol) can modulate eccrine activity and reduce emotionally driven (eg, anxiety) stimulation of eccrine sweating.

Educational objective:
Hyperthyroidism causes a hyperadrenergic state characterized by hypertension, palpitations/tachycardia, sweating, heat intolerance, tremor, and hyperreflexia. Beta blockers can relieve these symptoms. Exophthalmos in Graves disease is due to an immune-mediated increase in orbital soft tissue mass and does not improve with beta blockers.

References

- Short-term effects of ß-adrenergic antagonists and methimazole in new-onset thyrotoxicosis caused by Graves' disease.

Pharmacology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

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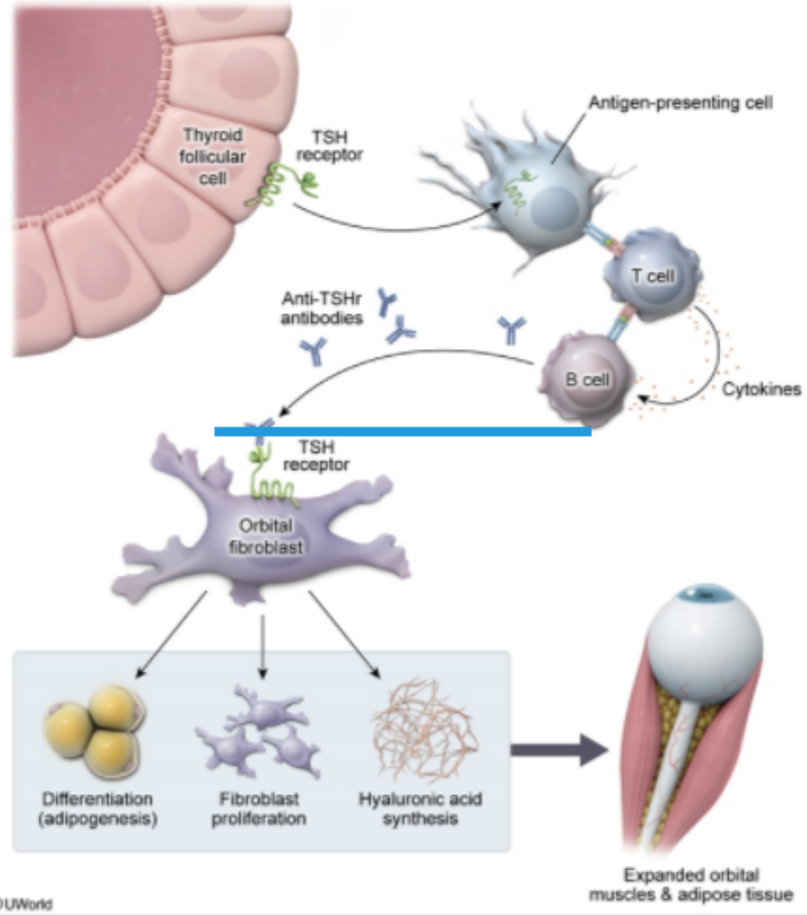
expression of **beta-adrenergic receptors** in various organs, and the subsequent hyperadrenergic state can result in hypertension, tremor, heat

Exhibit Display

Pathogenesis of Graves ophthalmopathy



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A 43-year-old woman volunteers for a clinical trial testing a medication for type 2 diabetes mellitus. She was diagnosed with diabetes mellitus 5 years ago, and her blood sugar has recently been uncontrolled despite taking the maximum tolerated dose of metformin. The subject's medical history is otherwise unremarkable, and she takes no concurrent medications that would disqualify her from enrolling in the trial. Initial laboratory studies show a fasting glucose of 155 mg/dL and hemoglobin A1c of 8.2%. A urine pregnancy test is negative, and other screening tests are normal. The study drug activates peroxisome proliferator-activated receptor gamma, a nuclear receptor and transcription factor. Activation of this receptor would most likely result in which of the following metabolic changes?

A. Decreased insulin resistance

B. Downregulation of adiponectin

C. Increased free fatty acid levels

D. Increased insulin release

E. Upregulation of leptin activity

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- ✓ A. Decreased insulin resistance (59%)
- B. Downregulation of adiponectin (10%)
- C. Increased free fatty acid levels (13%)
- D. Increased insulin release (11%)
- E. Upregulation of leptin activity (5%)

Omitted
Correct answer
A

59%
Answered correctly

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Explanation

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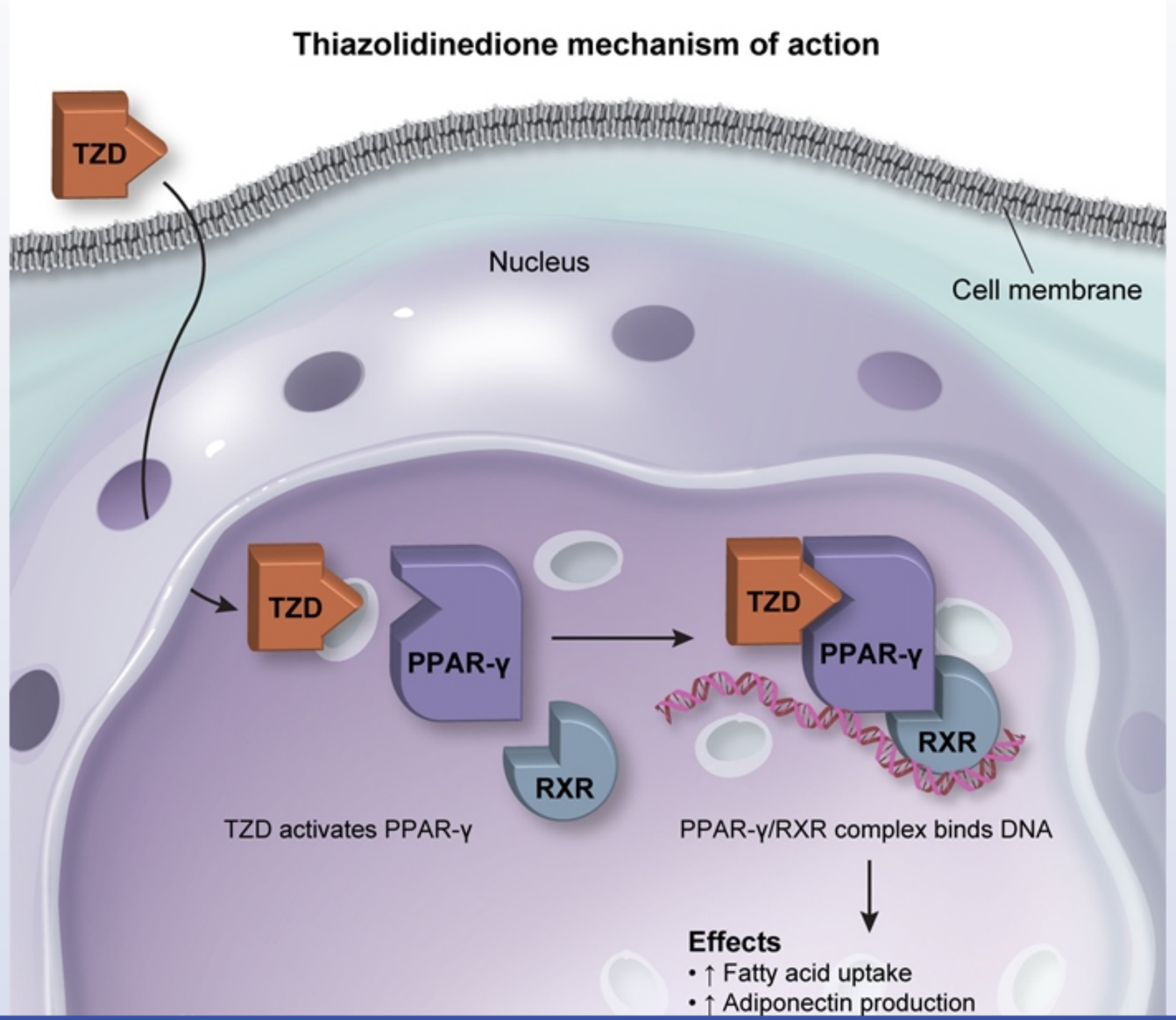

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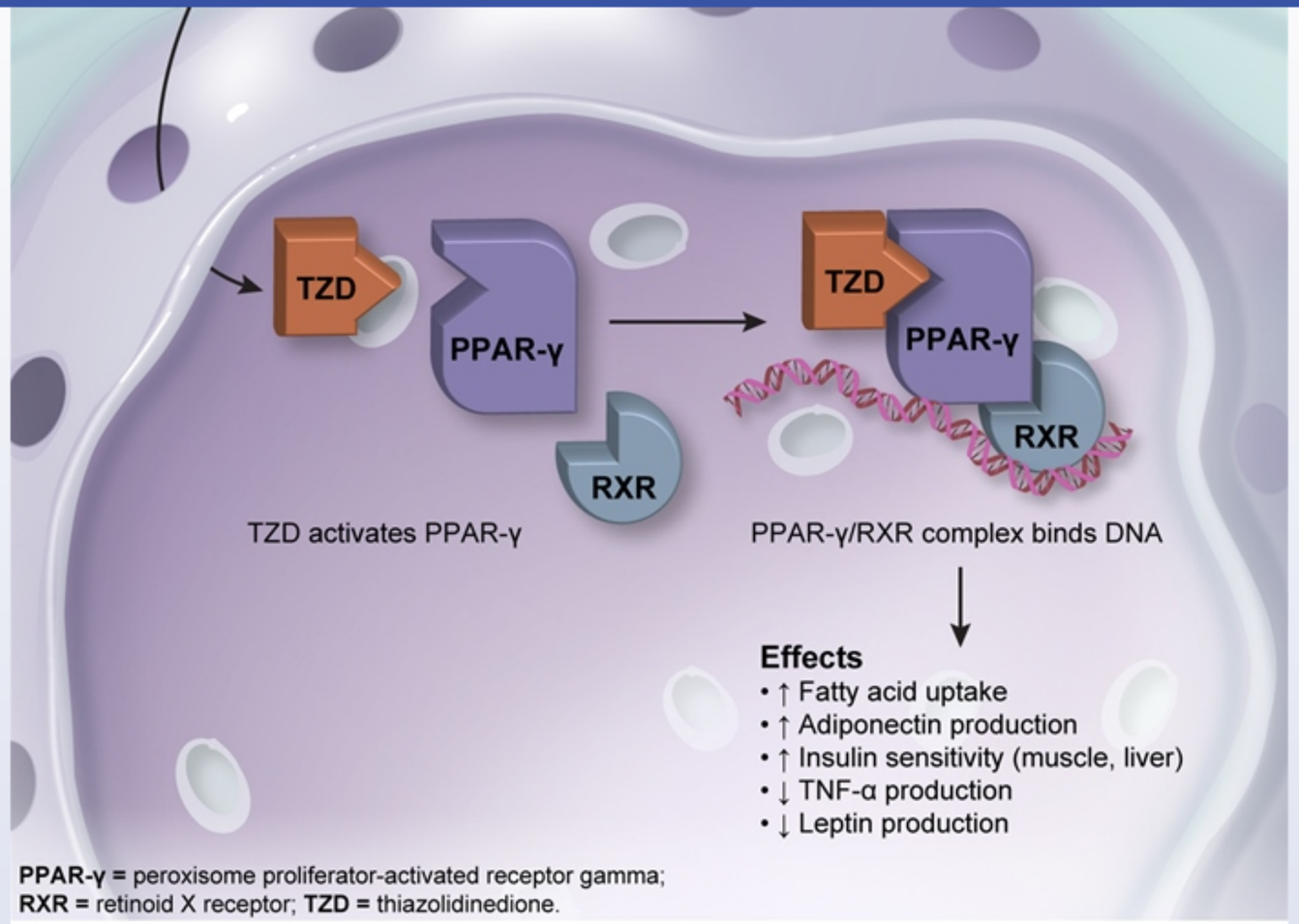

PPAR-γ = peroxisome proliferator-activated receptor gamma; **RXR** = retinoid X receptor; **TZD** = thiazolidinedione.

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This clinical trial is studying a **thiazolidinedione** (TZD), a class of medications that **decrease insulin resistance**. TZDs (eg, pioglitazone) bind to **peroxisome proliferator-activated receptor gamma** (PPAR-γ), a transcriptional regulator of genes involved in glucose and lipid metabolism. The activated complex then binds to the transcriptional regulatory sequence of target genes; important genes upregulated by TZDs include:

- **Glucose transporter-4**, an insulin-responsive, transmembrane glucose transporter expressed in adipocytes and skeletal myocytes that increases glucose uptake by target cells

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- **Glucose transporter-4**, an insulin-responsive, transmembrane glucose transporter expressed in adipocytes and skeletal myocytes that increases glucose uptake by target cells
- **Adiponectin**, a cytokine secreted by fat tissue that increases the number of insulin-responsive adipocytes and stimulates fatty acid oxidation **(Choice B)**

TZDs are functionally similar to fibrate medications (eg, fenofibrate, gemfibrozil), which bind PPAR-α and are effective in lowering blood triglyceride levels. The PPAR family of transcriptional regulators also plays a significant role in the pathogenesis of metabolic syndrome (obesity, hypertension, dyslipidemia, and insulin resistance).

(Choice C) PPAR-γ activation leads to an increase in fat mass secondary to the increased differentiation of preadipocytes into mature adipocytes. The increased movement of free fatty acids into fat cells, along with increased fatty acid oxidation (adiponectin effect), causes circulating free fatty acid levels to decrease.

(Choice D) TZDs do not stimulate insulin secretion; rather, as insulin resistance diminishes, circulating levels of insulin tend to decrease over time.

(Choice E) Leptin is a hormone secreted by fat cells that acts on the hypothalamus to decrease appetite. Although PPAR-γ activation increases fat cell mass, circulating leptin levels remain unchanged or decrease due to the inhibiting effect of PPAR-γ on leptin gene transcription.

Educational objective:
Thiazolidinediones (TZDs) lower blood glucose by decreasing insulin resistance. TZDs activate peroxisome proliferator-activated receptor gamma, a nuclear receptor that alters the transcription of genes involved in glucose and lipid metabolism.

References

- Minireview: challenges and opportunities in development of PPAR agonists.
- The roles of peroxisome proliferator-activated receptors in the metabolic syndrome.

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Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 60-year-old man comes to the office due to 2 months of low back pain unresponsive to over-the-counter analgesics. The pain is worse at night and interferes with sleep. On examination, the lumbar vertebrae are tender to palpation, and the prostate is indurated and firm. After a thorough evaluation, leuprolide therapy is started. Which of the following changes in testosterone (solid line) and dihydrotestosterone (dashed line) levels are most likely to occur in this patient after initiation of therapy?

- A.
- B.
- C.
- D.
- E.

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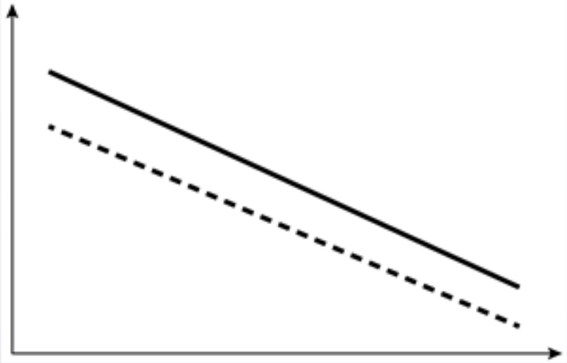

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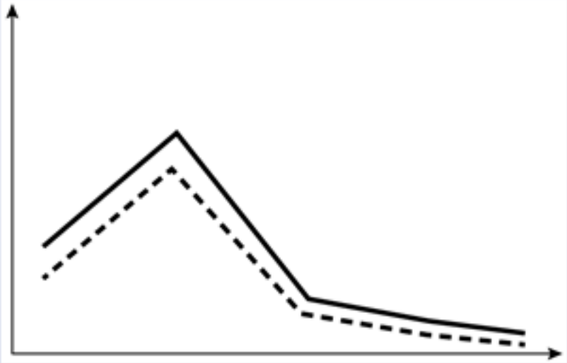

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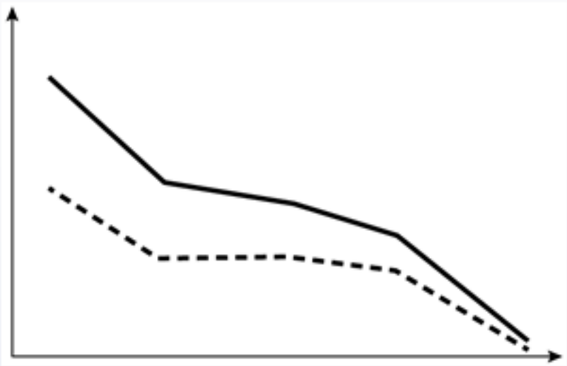

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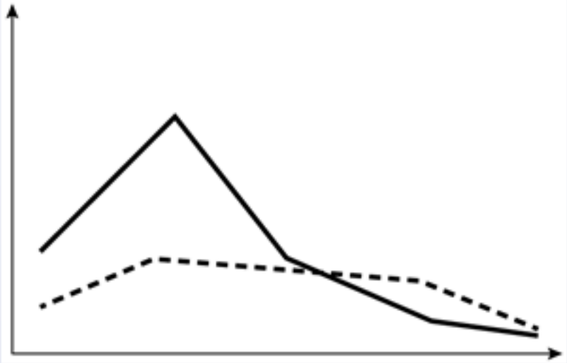

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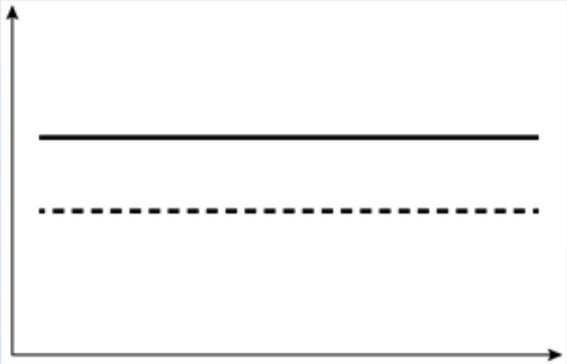

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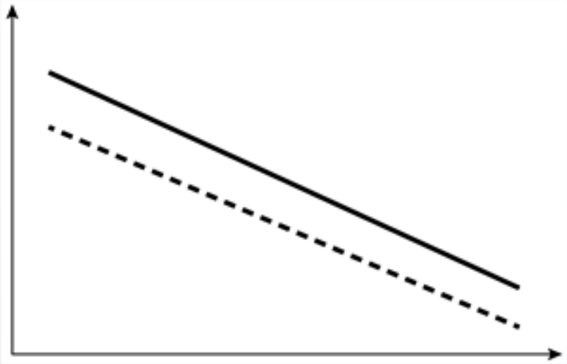
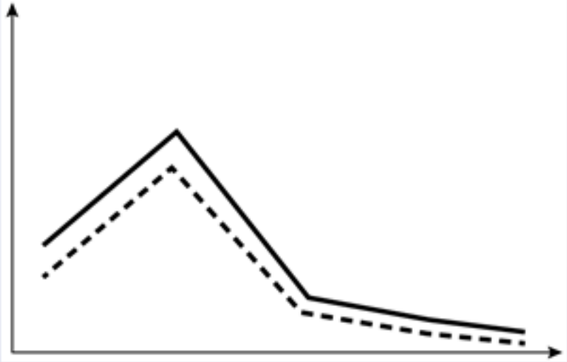
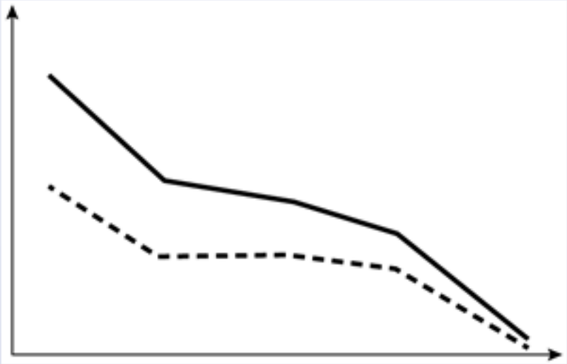
A.  (13%)

✓ B.  (59%)

C.  (8%)

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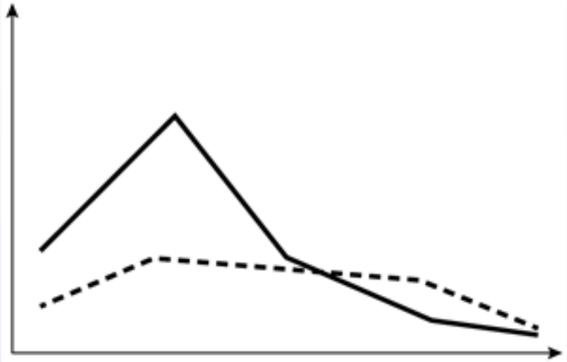

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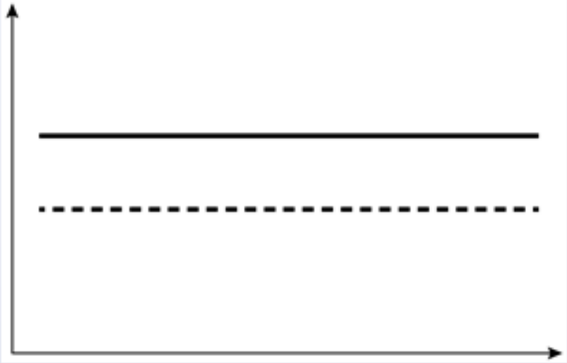

Omitted
Correct answer
B

59%
Answered correctly

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04/17/2020
Last Updated

Explanation

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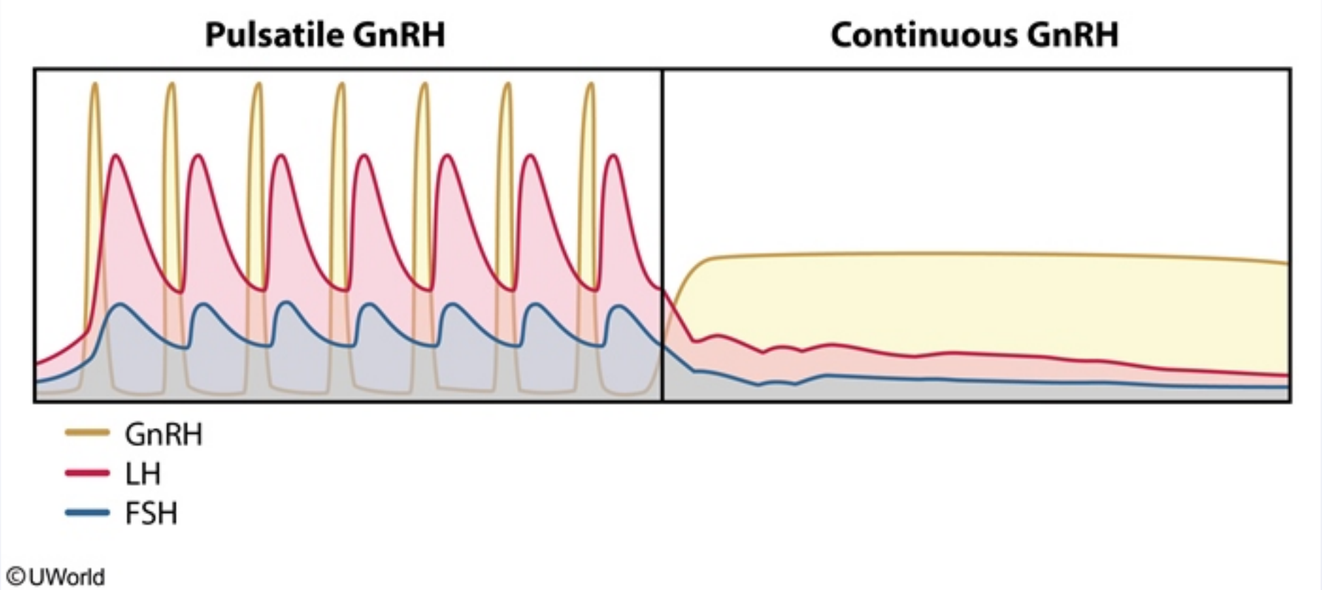

This patient's nocturnal back pain, spinal tenderness, and indurated prostate suggest **prostate adenocarcinoma** with bony metastases. Prostate cancer is an **androgen-dependent** tumor. Because most androgens (eg, testosterone) in men are made in the Leydig cells of the testes, initial treatment focuses on a systemic reduction in androgen production via surgical or medical **orchiectomy**.

Androgen production is primarily regulated by the hypothalamic-pituitary-testicular axis. Neurons in the hypothalamus release **GnRH** into the hypothalamic-pituitary portal system in a **pulsatile pattern** every 90-120 minutes. This stimulates pituitary gonadotrophs to release luteinizing hormone (**LH**) into the circulation, which then binds to a surface receptor on Leydig cells and stimulates androgen production.

In medical orchiectomy, a **GnRH analogue** (eg, **leuprolide**) is administered to continuously stimulate pituitary gonadotrophs, which leads to down-regulation of the GnRH receptor, lower LH release, and reduced testicular androgen production. However, because GnRH analogues **initially stimulate** pituitary gonadotrophs prior to the down-regulation of the receptor, most patients have a **transient increase in systemic androgens** during the first week of therapy (upward portion of graph). This effect is generally blunted by administering a short course of androgen receptor antagonist medication (eg, bicalutamide) during treatment initiation in order to prevent worsening of the underlying prostate cancer.

(Choices A and C) GnRH analogues stimulate the GnRH receptor prior to down-regulation, resulting in a transient increase in LH and systemic

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(Choices A and C) GnRH analogues stimulate the GnRH receptor prior to down-regulation, resulting in a transient increase in LH and systemic androgen production prior to down-regulation of the receptor.

(Choice D) The enzyme 5-alpha reductase converts testosterone to dihydrotestosterone (DHT) in peripheral tissues (eg, skin, liver); as testosterone levels fall, DHT production will decrease concurrently. GnRH analogues have no effect on the activity of 5-alpha reductase, therefore, testosterone and DHT levels rise and fall in synchrony following GnRH administration.

(Choice E) Benign prostatic hyperplasia is typically treated with a 5-alpha reductase inhibitor (eg, finasteride), which reduces the conversion of testosterone to DHT. This class of medications reduces DHT levels while testosterone levels remain largely unaffected.

Educational objective:
Leuprolide is a GnRH agonist used to treat prostate cancer. It initially stimulates pituitary LH secretion, which leads to a rise in androgen levels. However, the GnRH receptor is subsequently down-regulated, which dramatically drops LH release and leads to a long-term decrease in androgen production.

References

- Impact of surgical and medical castration on serum testosterone level in prostate cancer patients.

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A 47-year-old woman comes to the office for follow up of an asthma exacerbation. The patient was recently hospitalized and required a prolonged period of mechanical ventilation as well as nebulized bronchodilators and intravenous glucocorticoids. Her symptoms improved, and she was discharged on oral prednisone. The patient reports compliance with therapy. She has no other medical conditions and takes no other medications. Blood pressure is 128/72 mm Hg, pulse is 85/min, and respirations are 18/min. On physical examination, there is mild expiratory wheezing. Because of the persistent respiratory findings, the patient is continued on the same treatment regimen. Long-term administration of this oral therapy is most likely to increase which of the following in this patient?

A. Adrenocortical cell number
B. Dermal collagen synthesis
C. Expression of liver enzymes
D. Lymphoid cell formation
E. Muscle protein synthesis
F. Osteoblastic bone formation

Submit

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- A. Adrenocortical cell number (11%)
- B. Dermal collagen synthesis (13%)
- ✓ C. Expression of liver enzymes (46%)
- D. Lymphoid cell formation (9%)
- E. Muscle protein synthesis (9%)
- F. Osteoblastic bone formation (10%)

Omitted
Correct answer
C

46%
Answered correctly

02 secs
Time Spent

02/16/2020
Last Updated

Explanation

Effects of prolonged glucocorticoid therapy	
	• Lipolysis

Effects of prolonged glucocorticoid therapy	
Adipose	• Lipolysis • Altered fat distribution
Adrenal cortex	• Atrophy
Bone	• Osteoporosis
Immune system	• Suppression • T-cell apoptosis
Liver	• Increased gluconeogenesis & glycogenesis
Skeletal muscle	• Atrophy (glucocorticoid myopathy)
Skin	• Thinning • Stria • Impaired wound healing

Glucocorticoids are potent stimulators of liver **gluconeogenesis** and upregulate the synthesis of key gluconeogenic enzymes (eg, phosphoenolpyruvate carboxykinase, glucose-6-phosphatase). Glucocorticoids also increase hepatic **glycogen** reserves by increasing expression of glycogen synthase, thereby improving glucose availability during periods of acute stress. The increased demand for metabolic enzymes required for these actions leads to an overall **increase in liver protein synthesis**.

Peripherally, glucocorticoids antagonize the actions of insulin in skeletal muscle, favoring **catabolism** and proteolysis to provide substrates for gluconeogenesis and glycogenesis in the liver **(Choice E)**. This effect can manifest as proximal muscle weakness (glucocorticoid myopathy). The effect on adipose tissue is mixed, with lipolytic and antilipolytic effects, altered fat distribution (eg, central obesity, hypertrophy of the dorsocervical fat pad), and increased appetite and caloric intake. The net effect of gluconeogenesis and insulin antagonism is **hyperglycemia**.

(Choice A) Long-term glucocorticoid therapy causes atrophy of the adrenal cortex. On abrupt cessation, the delay in resumption of endogenous cortisol production can precipitate acute adrenal insufficiency.

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(Choice A) Long-term glucocorticoid therapy causes atrophy of the adrenal cortex. On abrupt cessation, the delay in resumption of endogenous cortisol production can precipitate acute adrenal insufficiency.

(Choice B) Glucocorticoids inhibit fibroblast proliferation and collagen formation in the skin. This results in thinning of the skin, impaired wound healing, and stria. The connective tissue that supports the capillaries is also thinned, leading to easy bruising.

(Choice D) Glucocorticoids are potent immunosuppressive agents. They increase expression of anti-inflammatory proteins but decrease expression of inflammatory proteins and cytokines and induce apoptosis in T cells (transient lymphopenia is common). Circulating neutrophil counts may increase in acute glucocorticoid administration due to increased release from bone marrow and "demargination" from peripheral tissues.

(Choice F) Glucocorticoids decrease bone mass by multiple mechanisms, including decreased gastrointestinal calcium absorption, increased renal calcium excretion, and direct inhibition of osteoblast activity.

Educational objective:
Glucocorticoids are predominantly catabolic, causing muscle weakness, skin thinning, impaired wound healing, osteoporosis, and immunosuppression. However, they also cause increased hepatic synthesis of gluconeogenic and glycogenic proteins to increase glucose availability. This, along with peripheral antagonism of insulin, contributes to the development of hyperglycemia.

References

- The effects of glucocorticoids on adipose tissue lipid metabolism.

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References

- The effects of glucocorticoids on adipose tissue lipid metabolism.

Pharmacology	Endocrine, Diabetes & Metabolism	Corticosteroids
Subject	System	Topic

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A 46-year-old man comes to the office to follow up mixed hyperlipidemia. His lipid levels have progressively worsened over the last 10 years associated with gradual weight gain. In the last 6 months, the patient has attempted to modify his diet and exercise regimen, but his lipid levels have not improved. Past medical history is unremarkable, and he currently takes no medications. The patient does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/86 mm Hg, pulse is 76/min, and BMI is 28 kg/m^2. Cardiovascular examination is normal. Which of the following drugs, when used as monotherapy, would be most likely to increase triglyceride levels in this patient?

A. Atorvastatin
B. Cholestyramine
C. Ezetimibe
D. Gemfibrozil
E. Niacin

Submit

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A. Atorvastatin (6%)
✓ B. Cholestyramine (47%)
C. Ezetimibe (13%)
D. Gemfibrozil (16%)
E. Niacin (15%)

Omitted
Correct answer
B

47%
Answered correctly

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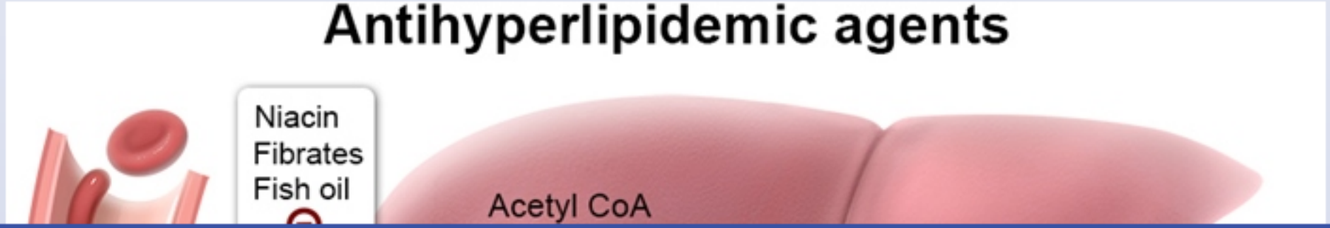
01/28/2020
Last Updated

Explanation



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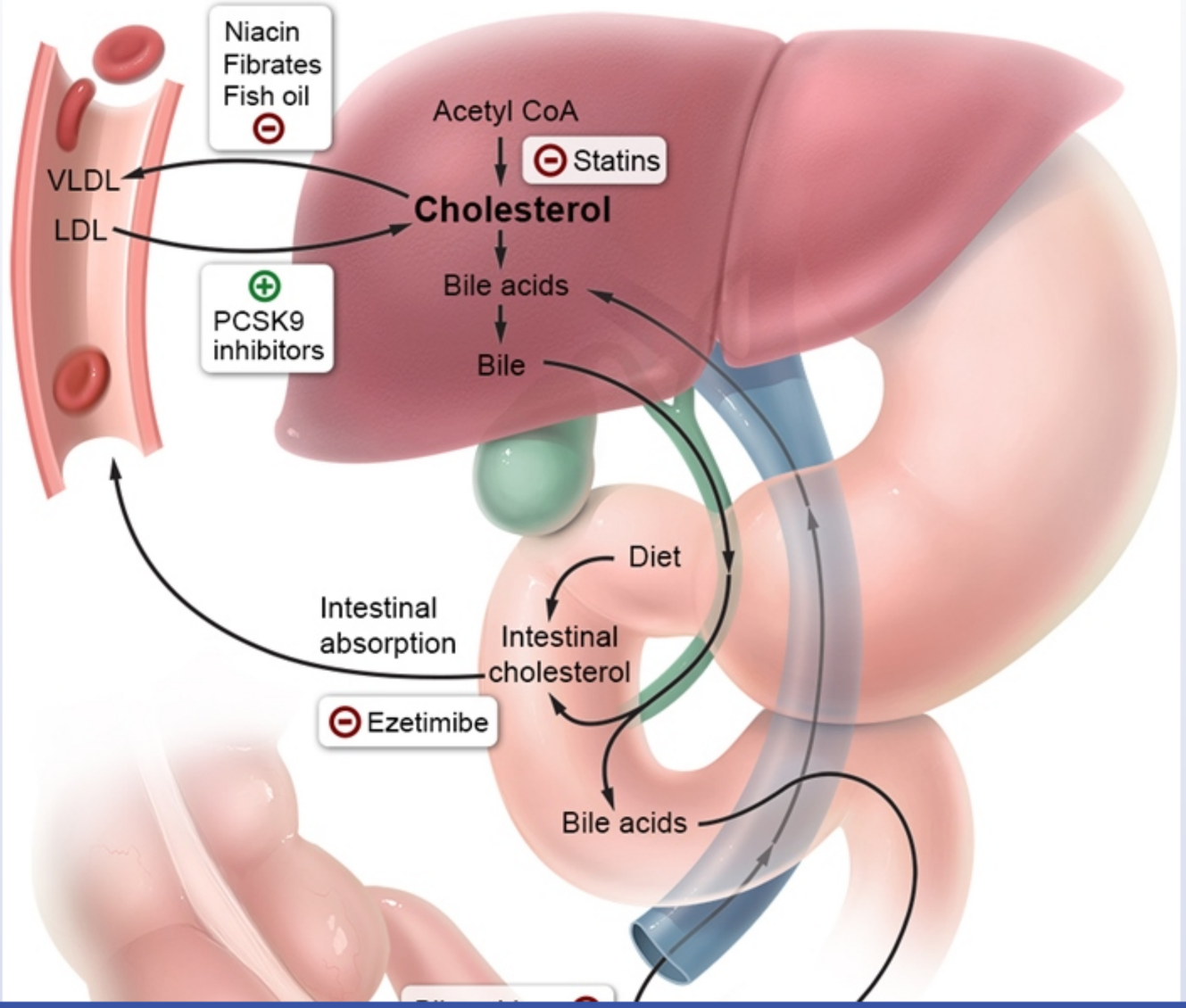
Antihyperlipidemic agents



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Bile acid-binding resins (eg, cholestyramine, colestipol, colesevelam) work by binding bile acids in the gastrointestinal tract, inhibiting **enterohepatic circulation**. This leads to diversion of hepatic cholesterol to synthesis of new bile acids, increased uptake of LDL cholesterol from the circulation, and reduced blood LDL levels.

The main side effects of bile acid-binding resins are gastrointestinal upset and impaired absorption of nutrients and drugs. In addition, bile acid-binding resins increase hepatic production of triglycerides and increase the release of triglyceride-heavy VLDL particles into the circulation, leading to **hypertriglyceridemia**.

(Choice A) Statins cause modest reductions in triglyceride levels by decreasing synthesis and increasing clearance of VLDL particles.

(Choice C) Ezetimibe selectively inhibits the intestinal absorption of cholesterol and lowers LDL levels. Ezetimibe does not affect triglyceride absorption but may lower blood triglyceride levels slightly.

(Choice D) Fibrates (eg, gemfibrozil, fenofibrate) inhibit hepatic production of triglycerides and are first-line treatments for hypertriglyceridemia.

(Choice E) Niacin reduces blood triglyceride levels, raises HDL levels, and decreases VLDL conversion to LDL, thereby decreasing LDL concentrations as well.

Educational objective:
Bile acid-binding resins inhibit the enterohepatic circulation of bile acids. This leads to diversion of hepatic cholesterol to synthesis of new bile acids, increased uptake of cholesterol from the circulation, and reduced blood LDL levels. However, bile acid-binding resins increase hepatic production of triglycerides and can cause hypertriglyceridemia.

Pharmacology	Endocrine, Diabetes & Metabolism	Dyslipidemia
Subject	System	Topic

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A 22-year-old man comes to the emergency department with abdominal pain and vomiting. His symptoms began acutely 24 hours ago with nausea and decreased appetite. His medical history is unremarkable. The patient drinks 3-4 beers a week and does not use tobacco or illicit drugs. BMI is 37 kg/m^2. Physical examination is notable for moderate epigastric tenderness with decreased bowel sounds but no rebound tenderness, guarding, or abdominal rigidity. Fasting laboratory studies show a serum triglyceride concentration of 1,500 mg/dL (normal: <200 mg/dL). Once the patient has been medically stabilized, which of the following medications would be most helpful in preventing recurrences of his condition?

A. Atorvastatin
B. Cholestyramine
C. Ezetimibe
D. Fenofibrate
E. Niacin
F. Omega-3 fatty acids

Submit

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- A. Atorvastatin (14%)
- B. Cholestyramine (7%)
- C. Ezetimibe (6%)
- ✓ D. Fenofibrate (59%)
- E. Niacin (11%)
- F. Omega-3 fatty acids (1%)

Omitted
Correct answer
D

59%
Answered correctly

02 secs
Time Spent

06/26/2020
Last Updated

Explanation

Antihyperlipidemic medications			
Drug	Mechanism	Major lipid effects	Side effects

Antihyperlipidemic medications			
Drug	**Mechanism**	**Major lipid effects**	**Side effects**
Statins	• Inhibit HMG-CoA reductase	• ↓↓ **LDL** • ↓ Triglycerides	• Hepatotoxicity • Muscle toxicity
Ezetimibe	• ↓ Intestinal cholesterol absorption	• ↓ LDL	• ↑ Hepatotoxicity if given with statins
Bile acid sequestrants	• Prevent reabsorption of bile acids in the intestine	• ↓ LDL	• Nausea, bloating, cramping • Impaired absorption of drug & fat-soluble vitamin
Niacin	• ↓ Fatty acid release • ↓ VLDL synthesis • ↓ HDL clearance	• ↓ LDL • ↑↑ HDL	• Flushing & pruritus • Hepatotoxicity • Hyperuricemia/gout
Fibrates	• Activate PPAR-α • ↓ VLDL synthesis	• ↓↓ **Triglycerides** • ↑ HDL	• Muscle toxicity • Gallstones
Fish oil/omega-3 fatty acids	• ↓ VLDL synthesis • ↓ Apolipoprotein B synthesis	• ↓ Triglycerides • ↑ HDL	• Fishy taste

PPAR-α = peroxisome proliferator-activated receptor-alpha.

This patient most likely has **acute pancreatitis** due to severe **hypertriglyceridemia**. Small quantities of pancreatic lipase normally leak into the pancreatic capillaries, where they can metabolize triglycerides to **free fatty acids**, which have toxic and inflammatory effects on the pancreas. The risk of pancreatitis rises with increasing triglyceride levels and is most significant when triglycerides are severely elevated (>1,000 mg/dL).

Triglycerides loosely reflect caloric balance; a calorie-restricted diet with increased exercise and reduced alcohol intake can provide a rapid and significant drop in triglyceride levels. Lipid-lowering medications are also indicated for patients with moderate to severe hypertriglyceridemia.

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Triglycerides loosely reflect caloric balance; a calorie-restricted diet with increased exercise and reduced alcohol intake can provide a rapid and significant drop in triglyceride levels. Lipid-lowering medications are also indicated for patients with moderate to severe hypertriglyceridemia. **Fibrates** (eg, fenofibrate, gemfibrozil) work by activating peroxisome proliferator-activated receptor-alpha (**PPAR-α**), which increases the synthesis of lipoprotein lipase.

(Choice A) Although statins (eg, atorvastatin) are the preferred lipid-lowering agents for the prevention of cardiovascular disease, they only modestly lower triglyceride levels and would be less effective than fibrates for preventing recurrent pancreatitis due to hypertriglyceridemia.

(Choices B and C) Bile acid-binding resins (eg, cholestyramine) work by binding bile acids in the gastrointestinal tract, subsequently interfering with enterohepatic bile acid circulation. Ezetimibe selectively inhibits intestinal cholesterol absorption. These medications are used primarily for the treatment of hypercholesterolemia.

(Choice E) Niacin decreases hepatic production of VLDLs and reduces triglyceride release from adipose tissue. It has a weaker effect in lowering triglycerides than fibrates and is associated with significant side effects, especially flushing.

(Choice F) Fish oil supplements containing omega-3 fatty acids lower triglyceride levels by decreasing the production of VLDLs. Fish oils decrease serum triglycerides to a lesser degree than fibrates but may be added to fibrates in patients whose triglyceride levels are not adequately controlled with a fibrate alone.

Educational objective:
In patients with severe hypertriglyceridemia, pancreatic lipases can cause toxic levels of free fatty acids to be released within the pancreatic tissue, leading to acute pancreatitis. Fibrates (eg, fenofibrate) are the most effective agents for the treatment of hypertriglyceridemia.

References

- Optimal pharmacologic approach to patients with hypertriglyceridemia and low high-density lipoprotein-cholesterol: randomized comparison of fenofibrate 160 mg and niacin 1500 mg.
- Familial dyslipidaemias: an overview of genetics, pathophysiology and management.

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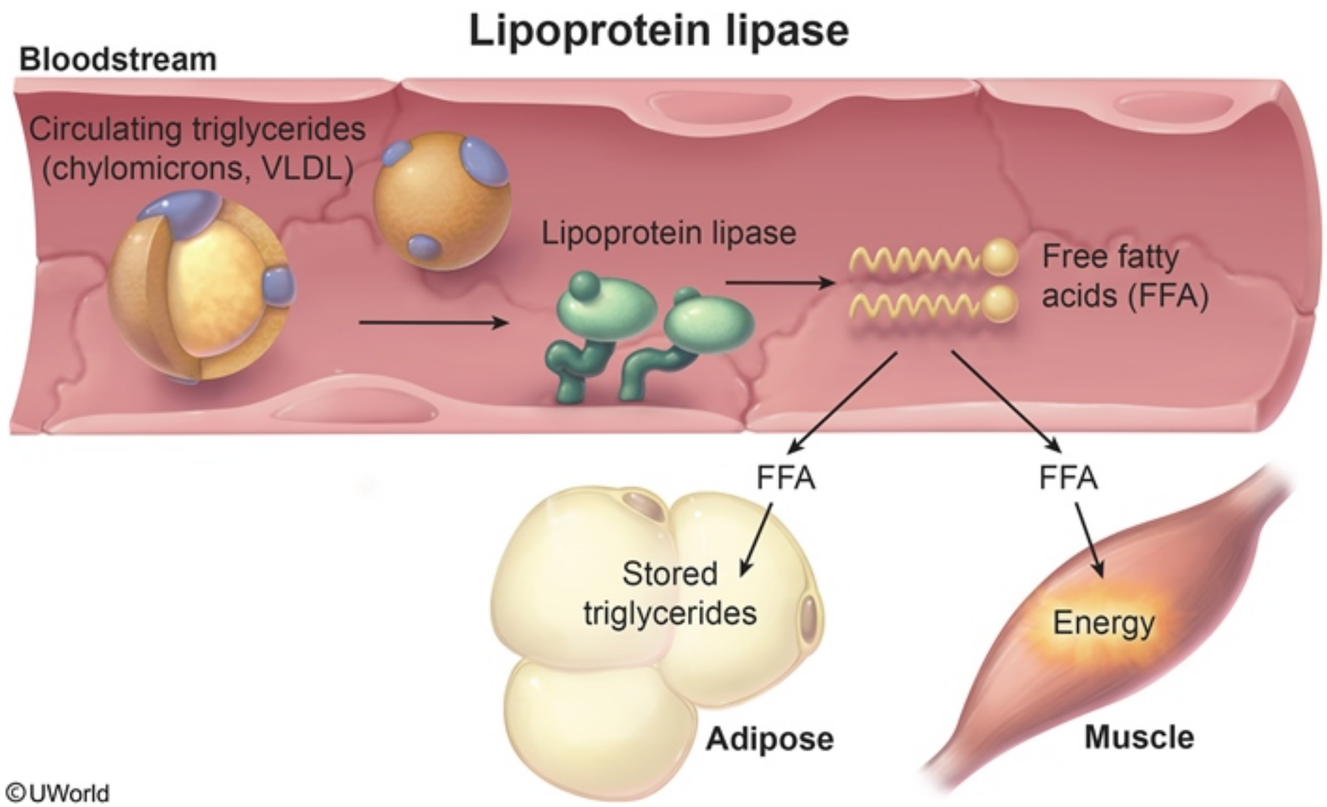
Exhibit Display



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(Choice F) Fish oil supplements containing omega-3 fatty acids lower triglyceride levels by decreasing the production of VLDLs. Fish oils decrease serum triglycerides to a lesser degree than fibrates but may be added to fibrates in patients whose triglyceride levels are not adequately controlled with a fibrate alone.

Educational objective:
In patients with severe hypertriglyceridemia, pancreatic lipases can cause toxic levels of free fatty acids to be released within the pancreatic tissue, leading to acute pancreatitis. Fibrates (eg, fenofibrate) are the most effective agents for the treatment of hypertriglyceridemia.

References

- Optimal pharmacologic approach to patients with hypertriglyceridemia and low high-density lipoprotein-cholesterol: randomized comparison of fenofibrate 160 mg and niacin 1500 mg.
- Familial dyslipidaemias: an overview of genetics, pathophysiology and management.
- Role of prescription omega-3 fatty acids in the treatment of hypertriglyceridemia.

Pharmacology	Endocrine, Diabetes & Metabolism	Acute pancreatitis
Subject	System	Topic

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A 48-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. She has had diabetes for 10 years with gradually worsening glycemic control despite taking multiple oral antidiabetic agents. Three months ago, the patient discontinued her oral medications (except for metformin) and started a daily injection of insulin glargine; she has had multiple visits with the diabetes educator since then to review injection technique and titrate up the dose. However, the patient reports a 4.5-kg (10-lb) weight gain since starting insulin. She says, "I feel like I need to eat more. If that's how insulin is going to be, then I don't want to continue it." Which of the following is the most appropriate response to this patient's statement?

A. "Regular exercise can reduce insulin-induced weight gain. What are your current exercise habits?"

B. "Some patients eat more after starting insulin because they fear their sugar may drop. Have you noticed that happening to you?"

C. "Sometimes stress can increase your appetite. How are things in your life right now?"

D. "Unfortunately, although insulin controls diabetes, it can cause weight gain. But the benefits outweigh the side effects."

Submit

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A. "Regular exercise can reduce insulin-induced weight gain. What are your current exercise habits?" (15%)

✓ B. "Some patients eat more after starting insulin because they fear their sugar may drop. Have you noticed that happening to you?" (49%)

C. "Sometimes stress can increase your appetite. How are things in your life right now?" (18%)

D. "Unfortunately, although insulin controls diabetes, it can cause weight gain. But the benefits outweigh the side effects." (16%)

Omitted
Correct answer
B

49%
Answered correctly

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05/06/2020
Last Updated

Explanation

Insulin-induced weight gain	
Physiologic factors	• Increased peripheral glucose uptake • Increased adipose fatty acid uptake • Reduced renal glucose losses

Insulin-induced weight gain	
Physiologic factors	• Increased peripheral glucose uptake • Increased adipose fatty acid uptake • Reduced renal glucose losses
Behavioral factors	• Less rigorous dietary adherence • Eating/snacking in response to hypoglycemic symptoms
Patient counseling	• Review for changes in diet • Ask about hypoglycemic symptoms

Insulin therapy for diabetes mellitus commonly causes **weight gain** due to increased peripheral glucose uptake, increased adipose lipid deposition, and reduced renal glucose loss (due to normalization of blood glucose, which reduces the filtered glucose load). Behavioral factors, including snacking and less rigorous adherence to dietary recommendations, can also contribute. Weight gain is especially pronounced in patients with type 2 diabetes who typically have high circulating levels of insulin and preexisting obesity.

This patient has experienced weight gain after initiating a long-acting insulin analogue (ie, insulin glargine). Insulin normally suppresses appetite, but this patient reports **increased need to eat**, which suggests that the weight gain may not be simply due to the metabolic effects of insulin. Specifically, this patient may be eating more to suppress **feelings of hypoglycemia**.

To address this patient's insulin-induced weight gain, the clinician should obtain additional history to elicit the **patient's perspective** on appetite, recent changes in **dietary patterns**, and associated **hypoglycemic symptoms**. Once the causes are better understood, several strategies, including dietary modification and changes to the insulin regimen, can mitigate insulin-induced weight gain.

(Choice A) Periodic review of exercise habits is recommended for patients with diabetes. However, this patient has already stated that appetite is her primary concern, so this should be explored first.

(Choice C) Patients can gain weight due to a variety of factors. In addition to physiologic factors, stress often alters diet and exercise habits, leading to weight gain. However, this patient's weight gain is temporally associated with the initiation and titration of insulin, which makes insulin the most reasonable culprit. If the issue is not resolved after addressing the patient's insulin regimen, other factors can be explored.

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To address this patient's insulin-induced weight gain, the clinician should obtain additional history to elicit the **patient's perspective** on appetite, recent changes in **dietary patterns**, and associated **hypoglycemic symptoms**. Once the causes are better understood, several strategies, including dietary modification and changes to the insulin regimen, can mitigate insulin-induced weight gain.

(Choice A) Periodic review of exercise habits is recommended for patients with diabetes. However, this patient has already stated that appetite is her primary concern, so this should be explored first.

(Choice C) Patients can gain weight due to a variety of factors. In addition to physiologic factors, stress often alters diet and exercise habits, leading to weight gain. However, this patient's weight gain is temporally associated with the initiation and titration of insulin, which makes insulin the most reasonable culprit. If the issue is not resolved after addressing the patient's insulin regimen, other factors can be explored.

(Choice D) Although the benefits of improved glycemic control with insulin generally outweigh the negative effects of weight gain, this statement does not address the patient's concerns and could miss an opportunity to improve the insulin program.

Educational objective:
Insulin can cause weight gain due to physiologic (eg, increased peripheral glucose uptake, reduced renal loss of glucose) and behavioral (eg, increased snacking in response to hypoglycemia, less rigorous attention to diet) factors. Counseling should elicit the patient's perspective on appetite, changes in dietary patterns, and hypoglycemic symptoms.

References

- Insulin-associated weight gain in obese type 2 diabetes mellitus patients: what can be done?

Pharmacology	Endocrine, Diabetes & Metabolism	Physician patient communication
Subject	System	Topic

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A 56-year-old man comes to the emergency department with acute onset of severe right foot pain. The pain is associated with local redness and swelling, but he has had no fever or recent trauma. The patient has never had similar symptoms. Medical history is significant for type 2 diabetes mellitus, mixed hyperlipidemia, hypertension, and coronary artery disease, for which he takes several medications. Physical examination shows a swollen, tender first metatarsophalangeal joint. Aspiration reveals a high leukocyte count, negative Gram stain, and numerous needle-shaped negatively birefringent crystals. Which of the following drugs is most likely to have precipitated this patient's condition?

A. Atorvastatin
B. Gemfibrozil
C. Hydrochlorothiazide
D. Losartan
E. Metformin

Submit

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- A. Atorvastatin (2%)
- B. Gemfibrozil (9%)
- ✓ C. Hydrochlorothiazide (82%)
- D. Losartan (1%)
- E. Metformin (3%)

Omitted
Correct answer
C

82%
Answered correctly

02 secs
Time Spent

03/31/2020
Last Updated

Explanation

Risk factors for gout	
Increased uric acid production	• Dietary sources ◦ Purine-rich foods (eg, seafood, red meat) ◦ Fructose-containing & alcoholic beverages (particularly beer)

Explanation

Risk factors for gout	

Increased uric acid production	• Dietary sources
	  ◦ Purine-rich foods (eg, seafood, red meat)
	  ◦ Fructose-containing & alcoholic beverages (particularly beer)
	• ↑ Cell turnover (eg, tumor lysis syndrome)
	• Lesch-Nyhan syndrome (deficiency of HGPRT)
	• ↑ Phosphoribosyl pyrophosphate activity

Decreased uric acid clearance	• Chronic kidney disease • Volume depletion • Diuretics (eg, thiazide) • Cyclosporine & tacrolimus
Rapid decline in uric acid levels	• Xanthine oxidase inhibitors (eg, allopurinol) • Uricosuric drugs (eg, probenecid)

HGPRT = hypoxanthine-guanine phosphoribosyltransferase.

This patient has an acute inflammatory arthritis of the first metatarsophalangeal joint with needle-shaped, **negatively birefringent** crystals noted on joint fluid microscopy. This presentation is consistent with an acute **gout flare**, which occurs due to the deposition of monosodium urate crystals within joint spaces (most commonly in the lower extremities).

Gout occurs in the setting of **hyperuricemia**, which may occur due to increased uric acid production (eg, dietary sources of purine) or reduced uric acid clearance. Most **diuretics** (eg, hydrochlorothiazide, furosemide) can cause hyperuricemia and trigger gout flares by causing relative **volume depletion**, which decreases the fractional excretion of uric acid. Other medications that can cause hyperuricemia include certain immunosuppressants (eg, cyclosporine, tacrolimus) and cytotoxic chemotherapeutic agents. In addition, medications that rapidly lower uric acid levels (eg, allopurinol) can paradoxically trigger an acute attack of gout due to mobilization of tissue urate stores (ie, dissolving crystals become fragile and more easily shed into the joint space).

HGPRT = hypoxanthine-guanine phosphoribosyltransferase.

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(Choices A and B) The lipid-lowering medication most prominently associated with gout is niacin, which decreases renal excretion of uric acid. Statins (eg, atorvastatin) can cause hepatitis and myalgias, and fibrates (eg, gemfibrozil, fenofibrate) can cause severe myopathy when given with statins; fibrates also increase the risk of cholesterol gallstones.

(Choice D) Losartan has a mild uricosuric effect and can be used in hypertensive patients with gout without precipitating an acute attack of gout.

(Choice E) Metformin slightly lowers uric acid, possibly due to changes in fatty acid metabolism. It is not associated with a significant risk of gout.

Educational objective:
Gout occurs in the setting of hyperuricemia and causes an inflammatory arthritis characterized by negative birefringent, needle-shaped crystals visible on joint fluid microscopy. Most diuretics (eg, hydrochlorothiazide, furosemide) can cause hyperuricemia and trigger gout flares by causing relative volume depletion, which decreases the fractional excretion of uric acid.

Pharmacology	Endocrine, Diabetes & Metabolism	Gout
Subject	System	Topic

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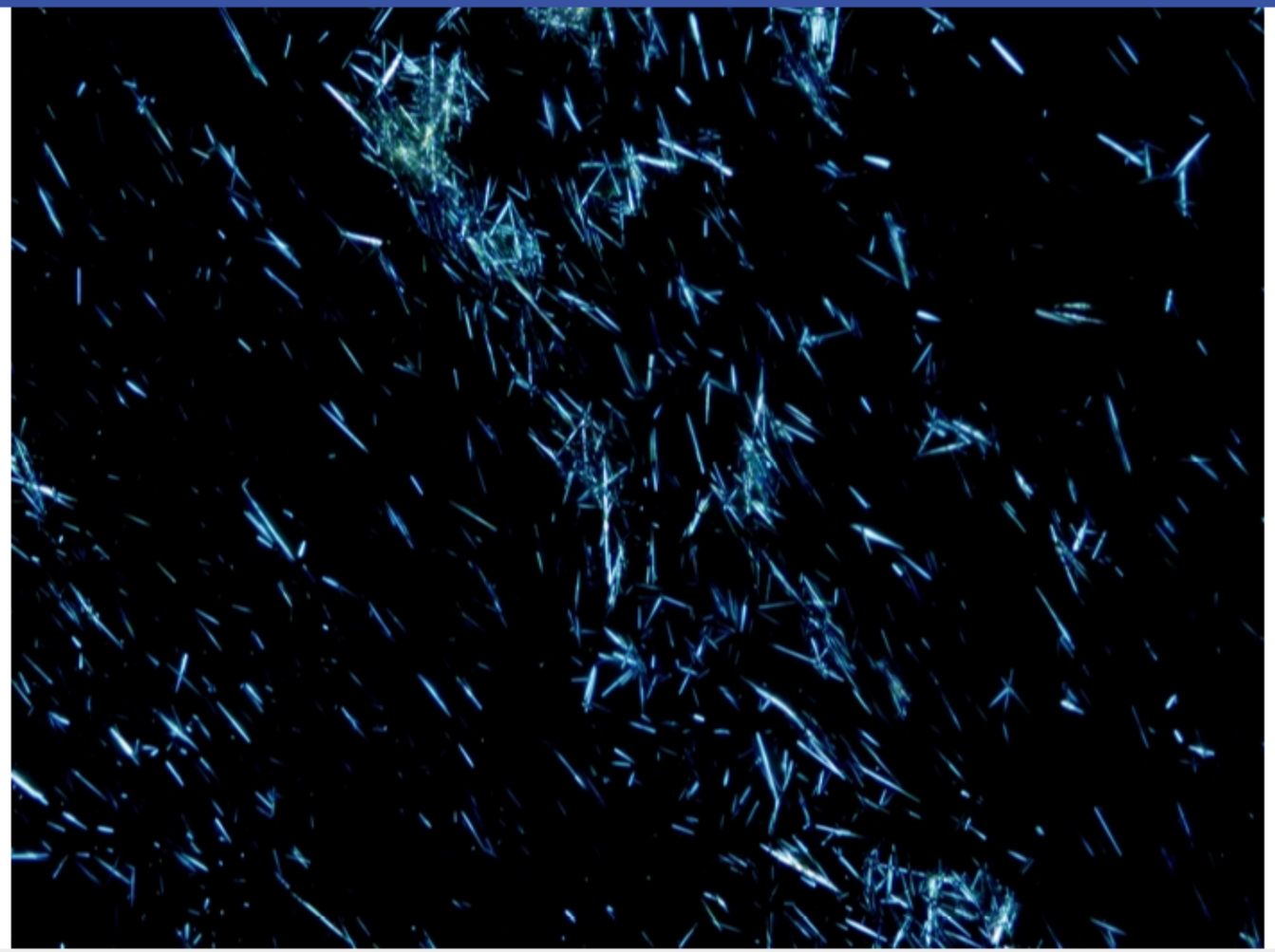

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A 28-year-old woman is treated with high-dose prednisone for severe lupus nephritis. Several hours after therapy is initiated, she becomes very agitated and delusional. Blood pressure is 130/70 mm Hg and heart rate is 110/min. A basic metabolic profile, complete blood cell (CBC) count, and urinalysis are obtained. The CBC differential is expected to show an increase in which of the following as a result of this patient's therapy?

A. Basophils
B. Eosinophils
C. Lymphocytes
D. Monocytes
E. Neutrophils

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A. Basophils (5%)
B. Eosinophils (16%)
C. Lymphocytes (13%)
D. Monocytes (8%)
✓ E. Neutrophils (57%)

Omitted
Correct answer
E

57%
Answered correctly

03 secs
Time Spent

07/07/2020
Last Updated

Explanation

Side effects of corticosteroids	
Skin/MSK	• Central obesity, buffalo hump • Skin atrophy, bruisability (↓collagen & fibroblasts) • Proximal muscle weakness
GI tract	Peptic ulcer, GI bleed (↓prostaglandins)

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Side effects of corticosteroids	
Skin/MSK	• Central obesity, buffalo hump • Skin atrophy, bruisability (↓collagen & fibroblasts) • Proximal muscle weakness
GI tract	• Peptic ulcer, GI bleed (↓prostaglandins)
Endocrine	• HPA axis suppression • Hyperglycemia • Hypogonadism • Osteoporosis (↓bone formation, ↓Ca/Phos absorption)
Immune	• Neutrophilia (neutrophil demargination) • Immunosuppression • ↑Risk of infection
Nervous	• Hypomania, psychosis • Sleep disturbance
Respiratory	• ↑Surfactant production

Ca = calcium; **GI** = gastrointestinal; **HPA** = hypothalamic-pituitary-adrenal; **MSK** = musculoskeletal; **Phos** = phosphate.

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As a result of their immunosuppressive effects, **corticosteroids** such as prednisone have been used to treat many autoimmune and inflammatory conditions, including systemic lupus erythematous. However, corticosteroid use can lead to a number of adverse effects. High doses can sometimes cause **corticosteroid-induced psychosis** (confusion, hallucinations), as seen in this patient; hypoalbuminemia is a risk factor, and

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As a result of their immunosuppressive effects, **corticosteroids** such as prednisone have been used to treat many autoimmune and inflammatory conditions, including systemic lupus erythematous. However, corticosteroid use can lead to a number of adverse effects. High doses can sometimes cause **corticosteroid-induced psychosis** (confusion, hallucinations), as seen in this patient; hypoalbuminemia is a risk factor, and the neuropsychiatric symptoms typically resolve with discontinuation of therapy.

Corticosteroid receptors also have widespread physiologic effects, including those on circulating leukocytes and vascular endothelial cells. **Neutrophil counts increase** following administration of the drug as a result of **"demargination"** of neutrophils previously attached to the vessel wall. Therefore, neutrophil recruitment to fight infection in tissues is decreased, potentially contributing to increased infection risk.

(Choice A) Corticosteroids reduce basophil count, which decreases local inflammatory responses by preventing histamine release.

(Choice B) Eosinophil counts decrease significantly with administration of corticosteroids (an effect previously used as the basis for a bioassay for corticosteroids). These drugs are used in allergic conditions as they reduce the eosinophil count and therefore the release of mediators from the eosinophils.

(Choice C) Corticosteroids reduce peripheral lymphocyte counts within minutes as a result of inhibition of immunoglobulin synthesis, stimulation of lymphocyte apoptosis, and lymphocyte redistribution (from the intravascular compartment to the spleen, lymph nodes, and bone marrow). T lymphocyte counts are typically reduced to a greater degree than B lymphocyte counts.

(Choice D) Corticosteroids inhibit peripheral extravasation of monocytes and macrophages and decrease antigen presentation by macrophages and dendritic cells. Blood monocyte levels drop after corticosteroid administration due to redistribution to lymphoid tissues.

Educational objective:
The acute effects of corticosteroids on the white blood cell count include an increased neutrophil count and decreased lymphocyte, monocyte, basophil, and eosinophil counts. The increase in the neutrophil count results from "demargination" of neutrophils previously attached to the vessel wall.

References

- A mechanism for the antiinflammatory effects of corticosteroids: the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1.

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Pharmacology	Endocrine, Diabetes & Metabolism	Corticosteroids
Subject	System	Topic

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In a series of animal experiments, the insulin concentration in the pancreatic veins is measured after the administration of various agents. Epinephrine administration is found to cause a decrease in insulin levels. However, after pretreatment with Drug A, epinephrine injection causes a paradoxical increase in insulin concentration. Which of the following receptors does Drug A most likely block?

A. Alpha-2 adrenergic receptors

B. Beta-2 adrenergic receptors

C. Glucagon-like peptide-1 receptors

D. Histamine H2 receptors

E. Muscarinic M3 receptors

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In a series of animal experiments, the insulin concentration in the pancreatic veins is measured after the administration of various agents. Epinephrine administration is found to cause a decrease in insulin levels. However, after pretreatment with Drug A, epinephrine injection causes a paradoxical increase in insulin concentration. Which of the following receptors does Drug A most likely block?

- A. Alpha-2 adrenergic receptors (41%)
- B. Beta-2 adrenergic receptors (37%)
- C. Glucagon-like peptide-1 receptors (18%)
- D. Histamine H2 receptors (0%)
- E. Muscarinic M3 receptors (1%)

Omitted
Correct answer
A

41%
Answered correctly

01 sec
Time Spent

07/04/2020
Last Updated

Explanation

G protein-coupled receptors on pancreatic beta cells

Receptor	G alpha subunit	Insulin secretion
Muscarinic M3	G_q	
Glucagon	G_s/ G_q	

G protein-coupled receptors on pancreatic beta cells		
Receptor	**G alpha subunit**	**Insulin secretion**
Muscarinic M3	G_q	↑
Glucagon	G_s/ G_q	
• Beta-2 adrenergic • Glucagon-like peptide-1	G_s	
• Alpha-2 adrenergic • Somatostatin 2	G_i	↓

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Pancreatic beta cell insulin secretion is influenced by serum glucose levels and other factors such as autonomic nervous system activity. Parasympathetic stimulation of muscarinic M3 receptors promotes insulin secretion and is induced by the smell and/or sight of food. In contrast, sympathetic stimulation is more complex, since both alpha-2 and beta-2 adrenergic receptors are present on pancreatic beta cells and exert opposite effects. Stimulation of beta-2 receptors promotes insulin secretion while stimulation of alpha-2 receptors inhibits insulin release. However, the alpha-2-mediated inhibitory effect is predominant, causing sympathetic stimulation to lead to overall inhibition of insulin secretion. Likewise, epinephrine administration activates both alpha-2 and beta-2 receptors, but the overriding inhibitory effect results in decreased insulin secretion. Following pretreatment with an alpha-2 receptor blocker (Drug A), epinephrine's effect on beta-2 receptors would become dominant, resulting in increased insulin secretion.

(Choice B) Stimulation of beta-2 adrenergic receptors results in increased insulin secretion; beta-2 receptor blockade would inhibit insulin release.

(Choice C) Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by the intestinal L cells in response to food and acts on receptors

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(Choice B) Stimulation of beta-2 adrenergic receptors results in increased insulin secretion; beta-2 receptor blockade would inhibit insulin release.

(Choice C) Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by the intestinal L cells in response to food and acts on receptors found on pancreatic beta cells to potentiate glucose-induced insulin release. Blocking GLP-1 receptors reduces insulin release. GLP-1 receptor agonists (eg, exenatide, liraglutide) are commonly used to treat type 2 diabetes mellitus.

(Choice D) Histamine H2 receptor stimulation increases insulin secretion. Blocking these receptors would cause a decrease in insulin release.

(Choice E) Parasympathetic stimulation increases insulin secretion via M3 muscarinic receptors. Blocking these receptors would inhibit the release of insulin.

Educational objective:
Alpha-2 adrenergic receptors inhibit insulin secretion, and beta-2 adrenergic receptors stimulate insulin secretion. The alpha-2-mediated inhibitory effect is generally predominant, causing sympathetic stimulation to lead to overall inhibition of insulin secretion.

References

- G-protein-coupled receptors and islet function-implications for treatment of type 2 diabetes.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 48-year-old man with type 2 diabetes mellitus comes to the office for a follow-up appointment. The patient was diagnosed 4 years ago and was initially managed with metformin, but that medication had to be discontinued due to diarrhea. He is currently being treated with the maximum therapeutic dose of glipizide, but has persistently elevated blood glucose levels. Laboratory results show a fasting blood glucose of 180 mg/dL and hemoglobin A1c of 8.6%. The patient does not want to take insulin or other injectable diabetic medications. After discussing various treatment options, canagliflozin is added to his current regimen. Which of the following tests should be ordered prior to initiating the new therapy in this patient?

A. Leukocyte count
B. Serum creatinine
C. Serum uric acid
D. Thyroid function tests
E. Urinalysis

Submit

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- A. Leukocyte count (4%)
- ✓ B. Serum creatinine (66%)
- C. Serum uric acid (4%)
- D. Thyroid function tests (3%)
- E. Urinalysis (21%)

Omitted
Correct answer
B

66%
Answered correctly

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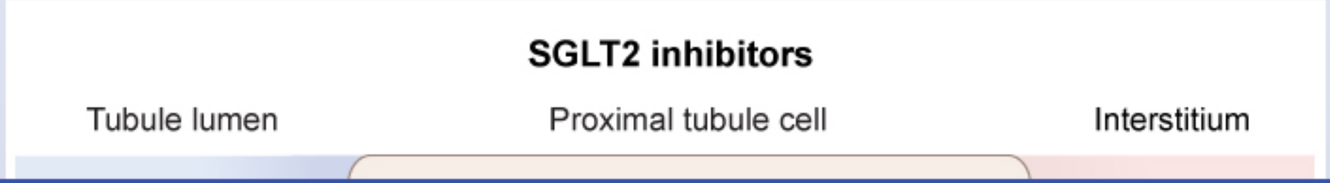
Time Spent

03/15/2020
Last Updated

Explanation



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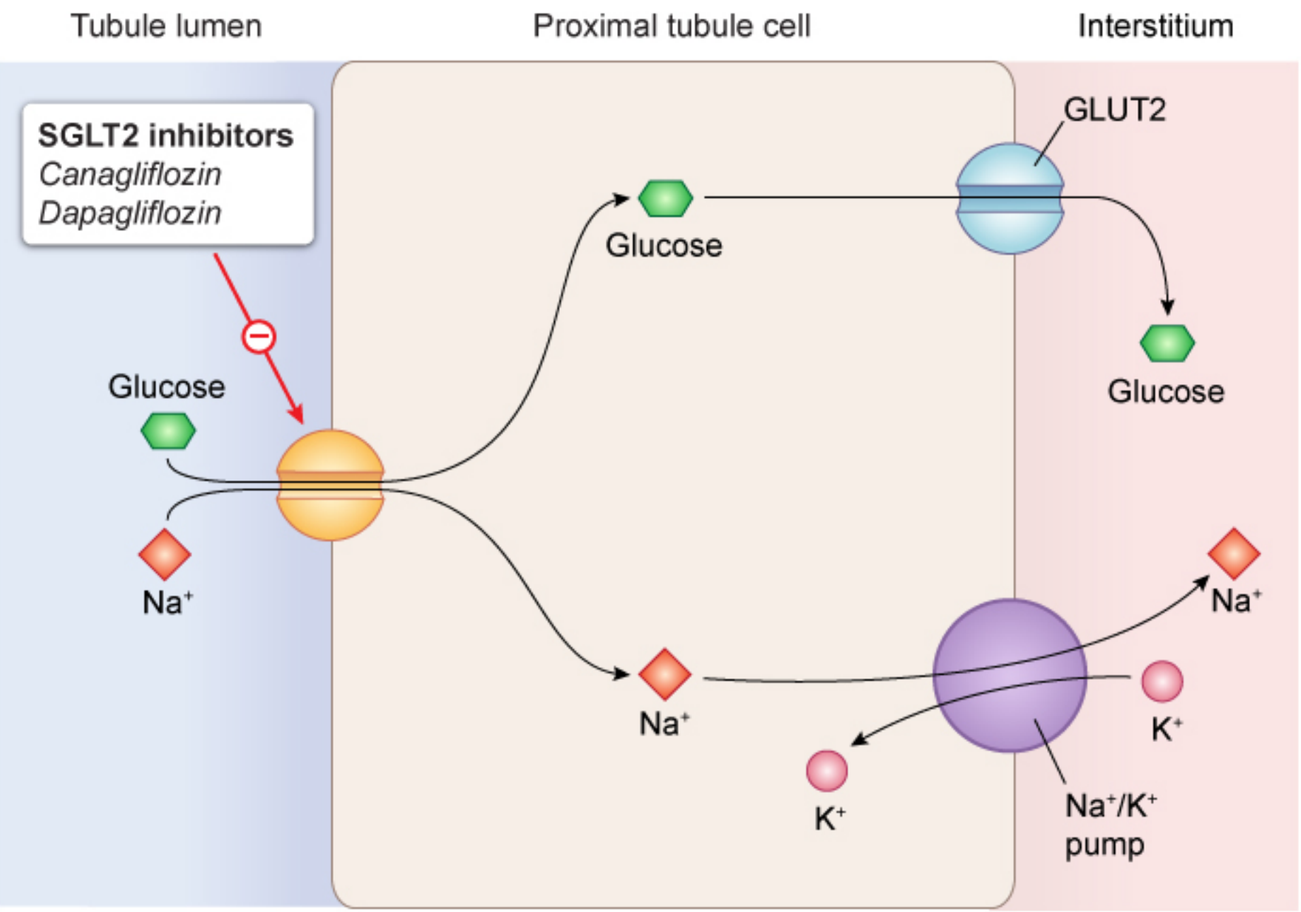
SGLT2 inhibitors



GLUT2 = glucose transporter 2; **SGLT2** = sodium-glucose cotransporter 2.

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Sodium-glucose cotransporter 2 (SGLT2) is a low-affinity, high-capacity transport protein that is responsible for reabsorbing 90% of filtered glucose in the proximal tubule. **SGLT2 inhibitors** (eg, canagliflozin, dapagliflozin) are oral antidiabetic agents that **decrease renal reabsorption of glucose**, leading to increased urinary glucose loss and decreased blood glucose levels. They are primarily used in patients who do not tolerate or have inadequate diabetic control with first-line medications (eg, metformin).

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The **effectiveness** of SGLT2 inhibitors is **dependent on glomerular filtration** of glucose, which is decreased in patients with chronic kidney disease. For this reason, an estimate of glomerular filtration with **serum creatinine** is recommended prior to initiation of therapy and periodically thereafter. Side effects include **genitourinary tract infections** due to glucosuria and moderate osmotic diuresis that can cause **symptomatic hypotension** (particularly in elderly individuals and patients taking diuretics).

(Choice A) A leukocyte count is not required before initiating treatment with antidiabetic agents.

(Choice C) Certain drugs such as diuretics (eg, thiazide, loop) and antituberculosis drugs (eg, pyrazinamide, ethambutol) reduce uric acid clearance and may precipitate gout. However, SGLT2 inhibitors are associated with increased uric acid excretion.

(Choice D) Thyroid function tests are routinely performed on patients taking lithium and amiodarone as these drugs can alter thryoid hormone metabolism. However, thyroid function tests are not required for antidiabetic medications.

(Choice E) Although SGLT2 inhibitors increase the risk of urinary tract infections, urinalysis prior to initiating therapy would not be of use.

Educational objective:
Sodium-glucose cotransporter 2 inhibitors (eg, canagliflozin, dapagliflozin) decrease renal reabsorption of glucose, leading to urinary glucose loss and decreased blood glucose levels. In patients with chronic kidney disease, these medications are less effective. Therefore, serum creatinine should be measured prior to therapy.

References

- A novel therapeutic agent for type 2 diabetes mellitus: SGLT2 inhibitor.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 34-year-old woman comes to the office due to inability to lose weight despite diet and exercise. She reports that she gained a significant amount of weight after she stopped smoking 4 years ago. The patient has tried several commercial weight-loss diet programs in the last year without success. She wants to lose at least 4.5 kg (10 lb) over the next few months before she gets married. The patient does not have any other medical conditions and takes no medications. Blood pressure is 122/80 mm Hg and pulse is 78/min. BMI is 33 kg/m^2. Physical examination shows an obese habitus but is otherwise unremarkable. Laboratory testing for secondary causes of weight gain is unrevealing. In addition to encouraging continued efforts at lifestyle change, the physician prescribes a short course of oral phentermine for weight loss. The weight loss induced by this medication is caused by which of the following mechanisms?

A. Delayed gastric emptying

B. Lipase inhibition

C. Opioid antagonist

D. Reduced presynaptic reuptake of serotonin

E. Release of norepinephrine

Submit

A 34-year-old woman comes to the office due to inability to lose weight despite diet and exercise. She reports that she gained a significant amount of weight after she stopped smoking 4 years ago. The patient has tried several commercial weight-loss diet programs in the last year without success. She wants to lose at least 4.5 kg (10 lb) over the next few months before she gets married. The patient does not have any other medical conditions and takes no medications. Blood pressure is 122/80 mm Hg and pulse is 78/min. BMI is 33 kg/m^2. Physical examination shows an obese habitus but is otherwise unremarkable. Laboratory testing for secondary causes of weight gain is unrevealing. In addition to encouraging continued efforts at lifestyle change, the physician prescribes a short course of oral phentermine for weight loss. The weight loss induced by this medication is caused by which of the following mechanisms?

A. Delayed gastric emptying (32%)
B. Lipase inhibition (10%)
C. Opioid antagonist (3%)
D. Reduced presynaptic reuptake of serotonin (6%)
✓ E. Release of norepinephrine (46%)

Omitted
Correct answer
E

46%
Answered correctly

02 secs
Time Spent

03/17/2020
Last Updated

Explanation

Medications for weight loss		
	Mechanism of action	Notable features

Medications for weight loss		
	Mechanism of action	**Notable features**
Sympathomimetic amines (ie, phentermine, diethylpropion, benzphetamine)	Stimulant/CAS	• High rate of weight regain • Not recommended for patients with CVD
Orlistat	Intestinal lipase inhibitor	• Significant gastrointestinal side effects
Bupropion/naltrexone	CAS (antidepressant + opioid antagonist)	• Lowers seizure threshold • May also assist in smoking cessation

CAS = central appetite suppressant; CVD = cardiovascular disease.

Norepinephrine-releasing agents (eg, **phentermine**) are sympathomimetic weight-loss drugs indicated for **short-term** (≤12 weeks) treatment of obesity. They work by stimulating release and inhibiting reuptake of norepinephrine and, to a lesser extent, serotonin and dopamine. Subjective effects include an **increased** sensation of **satiety** and subsequently reduced caloric intake.

Because of the increased sympathetic activity associated with these drugs, they can raise blood pressure and should be **avoided** in patients with comorbid **hypertension** or **heart disease**. Norepinephrine-releasing agents can induce brisk initial weight loss but are notable for poor long-term benefit, and most patients regain the lost weight following discontinuation.

(Choice A) Glucagonlike peptide-1 (GLP-1) agonists (eg, liraglutide) increase glucose-dependent insulin secretion and are most commonly used in treatment of type 2 diabetes mellitus. In addition, GLP-1 agonists cause delayed gastric emptying and decreased appetite, leading to weight loss.

(Choice B) Orlistat is an intestinal lipase inhibitor. It acts by reducing the digestion and subsequent absorption of dietary fats. The increased residual fat content in the intestinal lumen can lead to intestinal discomfort, diarrhea, fecal incontinence, and impaired absorption of fat-soluble vitamins (eg, vitamin D).

(Choice C) Naltrexone is an opioid antagonist indicated for the treatment of opioid abuse and alcohol dependence. It is also used in a

Norepinephrine-releasing agents (eg, **phentermine**) are sympathomimetic weight-loss drugs indicated for **short-term** (≤12 weeks) treatment of obesity. They work by stimulating release and inhibiting reuptake of norepinephrine and, to a lesser extent, serotonin and dopamine. Subjective effects include an **increased** sensation of **satiety** and subsequently reduced caloric intake.

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(Choice C) Naltrexone is an opioid antagonist indicated for the treatment of opioid abuse and alcohol dependence. It is also used in a combination pill with bupropion for weight loss, in which it is thought to potentiate the otherwise minor weight-loss effects of bupropion.

(Choice D) In addition to treating depression and anxiety, selective serotonin reuptake inhibitors (SSRIs) (eg, fluoxetine) are commonly used in the treatment of eating disorders, especially bulimia nervosa. Although some patients taking SSRIs experience minor weight loss, the effects on weight are variable, and these medications are not prescribed for weight loss.

Educational objective:
Norepinephrine-releasing agents (eg, phentermine) are sympathomimetic weight-loss drugs indicated for short-term treatment of obesity. They stimulate the release and inhibit the reuptake of norepinephrine. Subjective effects include an increased sensation of satiety, leading to reduced caloric intake. Weight regain after cessation is common with these drugs.

References

- Obesity pharmacotherapy.

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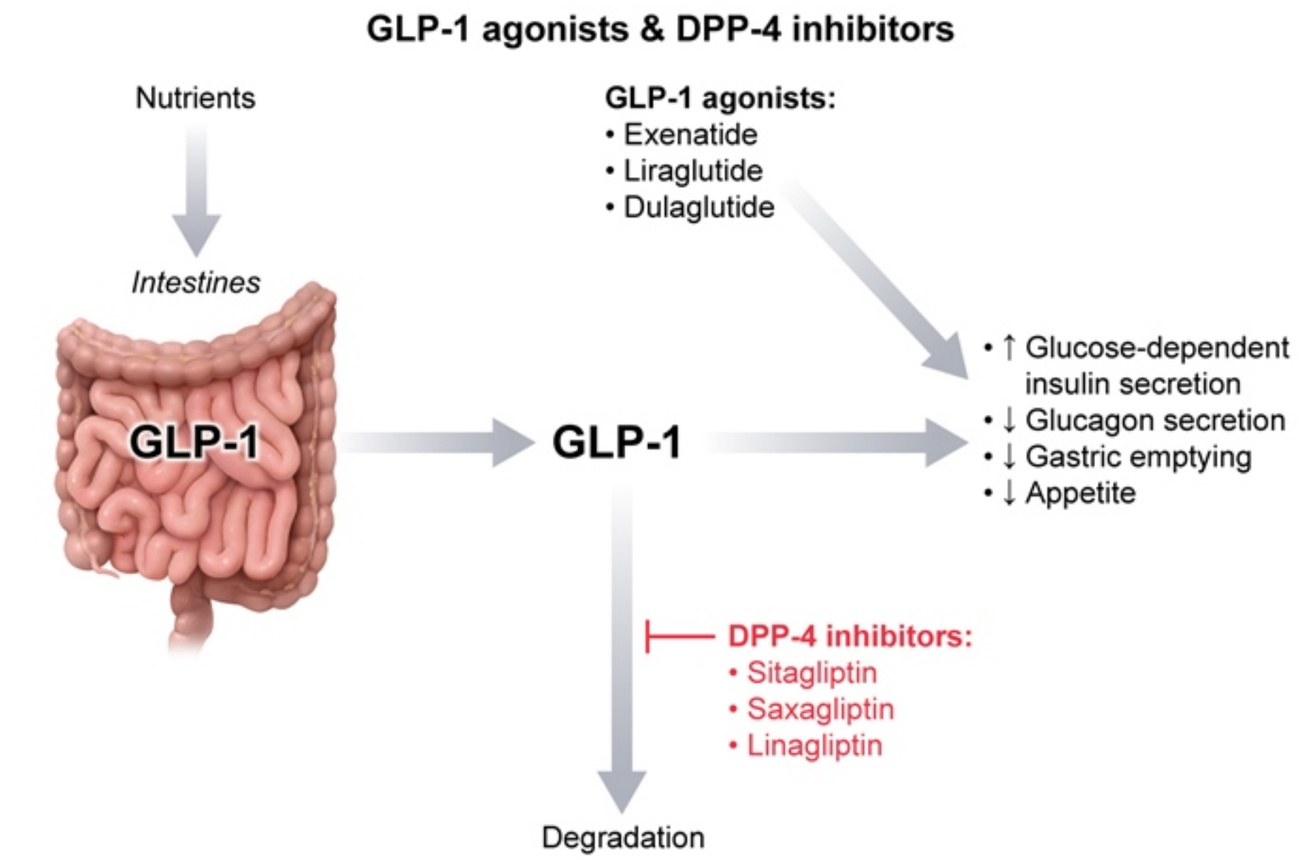
Exhibit Display



DDP-4 = dipeptidyl peptidase-4; **GLP-1** = glucagon like peptide-1.

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Because of the increased sympathetic activity associated with these drugs, they can raise blood pressure and should be **avoided** in patients with comorbid **hypertension** or **heart disease**. Norepinephrine-releasing agents can induce brisk initial weight loss but are notable for poor long-term benefit, and most patients regain the lost weight following discontinuation.

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References

- Obesity pharmacotherapy.

Pharmacology	Endocrine, Diabetes & Metabolism	Obesity
Subject	System	Topic

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A 68-year-old woman comes to the office due to a burning sensation in her chest and throat for the past 2 weeks. Associated symptoms include trouble swallowing. Medical history is significant for osteoporosis, and she has no known drug allergies. The patient has smoked half a pack of cigarettes daily for 50 years, and does not use alcohol or illicit drugs. Temperature is 36.7 C (98 F), blood pressure is 110/70 mm Hg, and pulse is 70/min. BMI is 20 kg/m^2. Cardiopulmonary examination shows clear lungs and normal S1 and S2. The abdomen is soft and nontender. Laboratory results are normal. It is determined that the patient's current symptoms are caused by one of her medications, which is discontinued. Her symptoms subsequently resolve. The medication responsible for this patient's presentation is also associated with which of the following side effects?

A. Chronic kidney disease

B. Hypercalcemia

C. Osteonecrosis of the jaw

D. Venous thromboembolism

E. Vitamin B_{12} deficiency

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- A. Chronic kidney disease (5%)
- B. Hypercalcemia (10%)
- ✓ C. Osteonecrosis of the jaw (78%)
- D. Venous thromboembolism (4%)
- E. Vitamin B_{12} deficiency (2%)

Omitted
Correct answer
C

78%
Answered correctly

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Time Spent

05/25/2020
Last Updated

Explanation

Medication-induced esophagitis	
Drug class	Drug

Medication-induced esophagitis	
Drug class	**Drug**
Antibiotics	Tetracyclines
Anti-inflammatory agents	Aspirin & many nonsteroidal anti-inflammatory drugs
Bisphosphonates	Alendronate, risedronate
Others	Potassium chloride, iron

This patient has esophagitis, with burning pain in the chest and dysphagia. **Medication-induced esophagitis** is a common adverse effect of **bisphosphonates** (eg, alendronate, risedronate) thought to be caused by disruption of the protective phospholipid barrier in the lower esophagus. This allows refluxing gastric acid to cause mucosal erosion and ulceration. Bisphosphonates are contraindicated in conditions that impair esophageal motility (eg, stricture, achalasia). When bisphosphonates are used, the risk of esophagitis can be lessened by taking the medication with a full glass of water (to ensure the pill is delivered fully into the stomach) and remaining upright for 30 minutes following administration (to avoid reflux of gastric contents).

Bisphosphonates are also associated with **osteonecrosis of the jaw** (mandible or maxilla) and atypical bone fractures (eg, stress fractures of the subtrochanteric zone and femoral shaft). The precise pathophysiology is debated and may vary, but proposed mechanisms include suppression of bone remodeling, impaired healing of microfractures, and decreased angiogenesis.

(Choice A) Medication-induced nephropathy can be due to interstitial nephritis (eg, cyclosporine), crystal nephropathy (eg, acyclovir), renal vasoconstriction (eg, amphotericin B, nonsteroidal anti-inflammatory drugs), or tubular injury (eg, aminoglycosides). Bisphosphonates are eliminated by the kidney and should be used with caution in patients with chronic kidney disease, but do not have substantial nephrotoxicity.

(Choice B) Bisphosphonates decrease bone resorption, thus lowering serum calcium levels. They are sometimes used in the treatment of severe hypercalcemia (eg, hypercalcemia of malignancy).

(Choice D) Venous thromboembolism is a recognized complication of selective estrogen receptor modulators (eg, raloxifene), but these

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(Choice B) Bisphosphonates decrease bone resorption, thus lowering serum calcium levels. They are sometimes used in the treatment of severe hypercalcemia (eg, hypercalcemia of malignancy).

(Choice D) Venous thromboembolism is a recognized complication of selective estrogen receptor modulators (eg, raloxifene), but these medications do not often cause esophagitis. Bisphosphonates do not appreciably increase the risk of thromboembolism.

(Choice E) Vitamin B_{12} deficiency can be seen in long-term proton pump inhibitor (eg, omeprazole) therapy, possibly due to decreased acid-dependent cleavage of vitamin B_{12} from dietary proteins. Although proton pump inhibitors may be taken by patients with bisphosphonate-induced esophagitis, bisphosphonates do not affect vitamin B_{12} metabolism.

Educational objective:
Medication-induced esophagitis is a common adverse effect of bisphosphonates. Bisphosphonates are also associated with increased risk of osteonecrosis of the jaw and atypical femoral fractures.

Pharmacology	Endocrine, Diabetes & Metabolism	Osteoporosis
Subject	System	Topic

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A 52-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. The patient was diagnosed with diabetes 6 months ago and initiated intensive lifestyle modification with increased exercise and a calorie-restricted diet; since that time, she has felt better subjectively but has lost only 2 kg (4.4 lb). Vital signs are normal. BMI is 35 kg/m^2. Fasting glucose is 155 mg/dL and hemoglobin A1c is 8.0%. Serum renal and liver function markers are normal. After discussion with the patient, metformin therapy is initiated. Which of the following physiologic changes are most likely to result as a direct effect of this medication?

	Hepatic gluconeogenesis	Muscle glucose uptake	Endogenous insulin production
A.	Decreased	Increased	Increased
B.	Decreased	Increased	Unchanged
C.	Decreased	Unchanged	Unchanged
D.	Unchanged	Increased	Unchanged
E.	Unchanged	Unchanged	Increased

Submit

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	Hepatic gluconeogenesis	Muscle glucose uptake	Endogenous insulin production
A.	Decreased (11%)	Increased	Increased
✓ B.	Decreased (67%)	Increased	Unchanged
C.	Decreased (16%)	Unchanged	Unchanged
D.	Unchanged (3%)	Increased	Unchanged
E.	Unchanged (0%)	Unchanged	Increased

Omitted
Correct answer
B

67%
Answered correctly

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04/17/2020
Last Updated

Explanation

Metformin	
Mechanism of action	• Inhibits mitochondrial glycerophosphate dehydrogenase & complex I • Upregulates AMP-activated protein kinase
Metabolic effects	• ↓ Hepatic glucose production • ↓ Intestinal glucose absorption • ↑ Peripheral glucose uptake/utilization • ↓ Lipogenesis
Pharmacokinetics	• Renal clearance • No significant metabolites
Adverse effects	• Diarrhea • Lactic acidosis • Vitamin B_{12} deficiency
Precautions/ contraindications	• Renal insufficiency (check serum creatinine) • Hepatic insufficiency • Congestive heart failure

This patient has uncontrolled type 2 diabetes mellitus and is appropriately given metformin, which is the preferred first-line medication for most patients. **Metformin** has a number of important metabolic effects:

- **Reduced hepatic gluconeogenesis** and release of glucose into circulation: Metformin inhibits glycerophosphate dehydrogenase and complex I (mitochondrial enzymes), which reduces the availability of substrates for gluconeogenesis (eg, glycerol, lactate).
- **Increased insulin-dependent peripheral glucose uptake** and utilization.
- Reduced circulating lipid levels: Metformin upregulates AMP-activated protein kinase in hepatocytes, which inhibits lipogenesis.

Circulating levels of endogenous insulin are unchanged or slightly decreased by metformin; therefore, metformin carries **low risk of hypoglycemia**. In addition, it reduces caloric intake due to decreased appetite and decreased absorption of glucose, leading to modest **weight**

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- **Increased insulin-dependent peripheral glucose uptake** and utilization.
- Reduced circulating lipid levels: Metformin upregulates AMP-activated protein kinase in hepatocytes, which inhibits lipogenesis.

Circulating levels of endogenous insulin are unchanged or slightly decreased by metformin; therefore, metformin carries **low risk of hypoglycemia**. In addition, it reduces caloric intake due to decreased appetite and decreased absorption of glucose, leading to modest **weight loss** in most patients.

(Choice A) Sulfonylureas (eg, glyburide, glimepiride) stimulate beta cell insulin release, leading to decreased glycogenolysis and gluconeogenesis and increased peripheral uptake of glucose; the higher circulating insulin levels also confer an increased risk of hypoglycemia and weight gain.

Educational objective:
Metformin reduces hepatic gluconeogenesis and release of glucose into circulation; increases peripheral glucose uptake and utilization; and reduces circulating lipid levels. Circulating insulin levels are unchanged or slightly decreased; therefore, metformin carries low risk of hypoglycemia. In addition, metformin reduces caloric intake due to decreased appetite and decreased absorption of glucose, leading to modest weight loss.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 44-year-old man comes to the office for follow-up of type 2 diabetes mellitus. He was diagnosed with diabetes 4 years ago and has been taking metformin since then. Six months ago, a new antidiabetic agent was added due to suboptimal glycemic control. Today, the patient is happy because he has lost 7 kg (15.4 lb) without any changes in diet or activity since the new therapy was started. His only symptoms are occasional nausea, vomiting, and a prolonged sensation of fullness after eating. Vital signs are within normal limits with no orthostatic changes. BMI is 34 kg/m^2. Physical examination shows normal heart and lung sounds, a nontender abdomen, and normal deep tendon reflexes and sensory examination. Laboratory testing reveals normal renal function studies and hemoglobin A1c of 7.2%. If this patient's weight loss is due to the new medication, which of the following agents is most likely responsible?

- A. Basal-bolus insulin therapy
- B. Dipeptidyl peptidase-4 inhibitor
- C. Glucagon-like peptide-1 agonist
- D. Sulfonylurea
- E. Thiazolidinedione

Submit

A 44-year-old man comes to the office for follow-up of type 2 diabetes mellitus. He was diagnosed with diabetes 4 years ago and has been taking metformin since then. Six months ago, a new antidiabetic agent was added due to suboptimal glycemic control. Today, the patient is happy because he has lost 7 kg (15.4 lb) without any changes in diet or activity since the new therapy was started. His only symptoms are occasional nausea, vomiting, and a prolonged sensation of fullness after eating. Vital signs are within normal limits with no orthostatic changes. BMI is 34 kg/m^2. Physical examination shows normal heart and lung sounds, a nontender abdomen, and normal deep tendon reflexes and sensory examination. Laboratory testing reveals normal renal function studies and hemoglobin A1c of 7.2%. If this patient's weight loss is due to the new medication, which of the following agents is most likely responsible?

- A. Basal-bolus insulin therapy (3%)
- B. Dipeptidyl peptidase-4 inhibitor (17%)
- ✓ C. Glucagon-like peptide-1 agonist (59%)
- D. Sulfonylurea (9%)
- E. Thiazolidinedione (9%)

Omitted
Correct answer
C

59%
Answered correctly

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Time Spent

04/07/2020
Last Updated

Explanation

Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	Mechanism of action	Side effects

Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	**Mechanism of action**	**Side effects**
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
Biguanides • Metformin	Stimulate AMPK & inhibit mitochondrial gluconeogenesis, ↓ hepatic glucose production & ↑ peripheral glucose uptake	• Diarrhea • Lactic acidosis
Thiazolidinediones • Pioglitazone	Activate transcription regulator PPAR-γ, ↓ insulin resistance	• Fluid retention/heart failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
α-glucosidase inhibitors • Acarbose • Miglitol	↓ Intestinal disaccharide absorption	• Diarrhea • Flatulence
SGLT2 inhibitors		• Urinary tract

• Liraglutide		
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
α-glucosidase inhibitors • Acarbose • Miglitol	↓ Intestinal disaccharide absorption	• Diarrhea • Flatulence
SGLT2 inhibitors • Canagliflozin • Dapagliflozin	↑ Renal glucose excretion	• Urinary tract infections • Hypotension
AMPK = adenosine monophosphate–activated protein kinase; **DPP4** = dipeptidyl peptidase-4; **GIP** = gastric inhibitory polypeptide; **GLP-1** = glucagonlike peptide-1; K_{ATP} = ATP-sensitive potassium; **PPAR-γ** = peroxisome proliferator–activated receptor γ; **SGLT2** = sodium-glucose cotransporter 2.		

This patient with uncontrolled diabetes on metformin therapy was started on a second medication to improve his glycemic control. The new agent was associated with significant **weight loss**, a side effect that is characteristic of **glucagon-like peptide-1 (GLP-1) agonists** (eg, exenatide, liraglutide).

GLP-1 is secreted by intestinal L cells in response to food intake and regulates glucose by slowing gastric emptying, suppressing glucagon secretion, and **increasing glucose-dependent insulin release**. It acts through cell surface receptors that are coupled with a G protein–adenylyl cyclase system. Native GLP-1 is degraded by dipeptidyl peptidase-4 (DPP-4), but synthetic GLP-1 agonists are resistant to degradation, allowing for a prolonged therapeutic effect.

Although insulin secretion is increased by GLP-1 agonists, most patients lose weight due to **enhanced satiety** and a **prolonged feeling of fullness** following meals; this effect is also seen in patients who do not have diabetes. GLP-1 agonists are administered parenterally. Adverse effects include nausea and vomiting (due to delayed gastric emptying) and pancreatitis, but the risk of hypoglycemia is low because insulin secretion is not stimulated when circulating glucose levels are normal.

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Although insulin secretion is increased by GLP-1 agonists, most patients lose weight due to **enhanced satiety** and a **prolonged feeling of fullness** following meals; this effect is also seen in patients who do not have diabetes. GLP-1 agonists are administered parenterally. Adverse effects include nausea and vomiting (due to delayed gastric emptying) and pancreatitis, but the risk of hypoglycemia is low because insulin secretion is not stimulated when circulating glucose levels are normal.

(Choice A) Basal-bolus insulin therapy is effective in patients with even the most poorly controlled diabetes (eg, hemoglobin A1c >10%). It has few side effects but is typically associated with significant weight gain.

(Choice B) DPP-4 inhibitors (eg, sitagliptin) are oral agents that block degradation of endogenous GLP-1. They share several side effects with GLP-1 agonists (eg, nausea), but are generally less potent and typically do not induce noticeable weight loss.

(Choice D) Sulfonylureas directly stimulate pancreatic insulin secretion independent of circulating glucose levels. They typically cause weight gain and carry a risk of hypoglycemia.

(Choice E) Thiazolidinediones (eg, pioglitazone) are peroxisome proliferator–activated receptor-gamma agonists that increase transcription of certain insulin-responsive genes and decrease insulin resistance. Because they do not promote insulin release, they do not cause hypoglycemia, but common side effects include fluid retention and weight gain.

Educational objective:
Glucagon-like peptide-1 (GLP-1) is secreted by intestinal L cells in response to food intake and regulates glucose levels by slowing gastric emptying, suppressing glucagon secretion, and increasing glucose-dependent insulin release. GLP-1 agonists are parenteral antidiabetic agents that can improve glycemic control with low risk of hypoglycemia. They are also associated with significant weight loss unlike many other antidiabetic agents.

References

- GLP-1 receptor agonists: nonglycemic clinical effects in weight loss and beyond.

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References

- GLP-1 receptor agonists: nonglycemic clinical effects in weight loss and beyond.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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AMPK = adenosine monophosphate–activated protein kinase; DPP4 = dipeptidyl peptidase-4; GIP = gastric inhibitory polypeptide; GLP-

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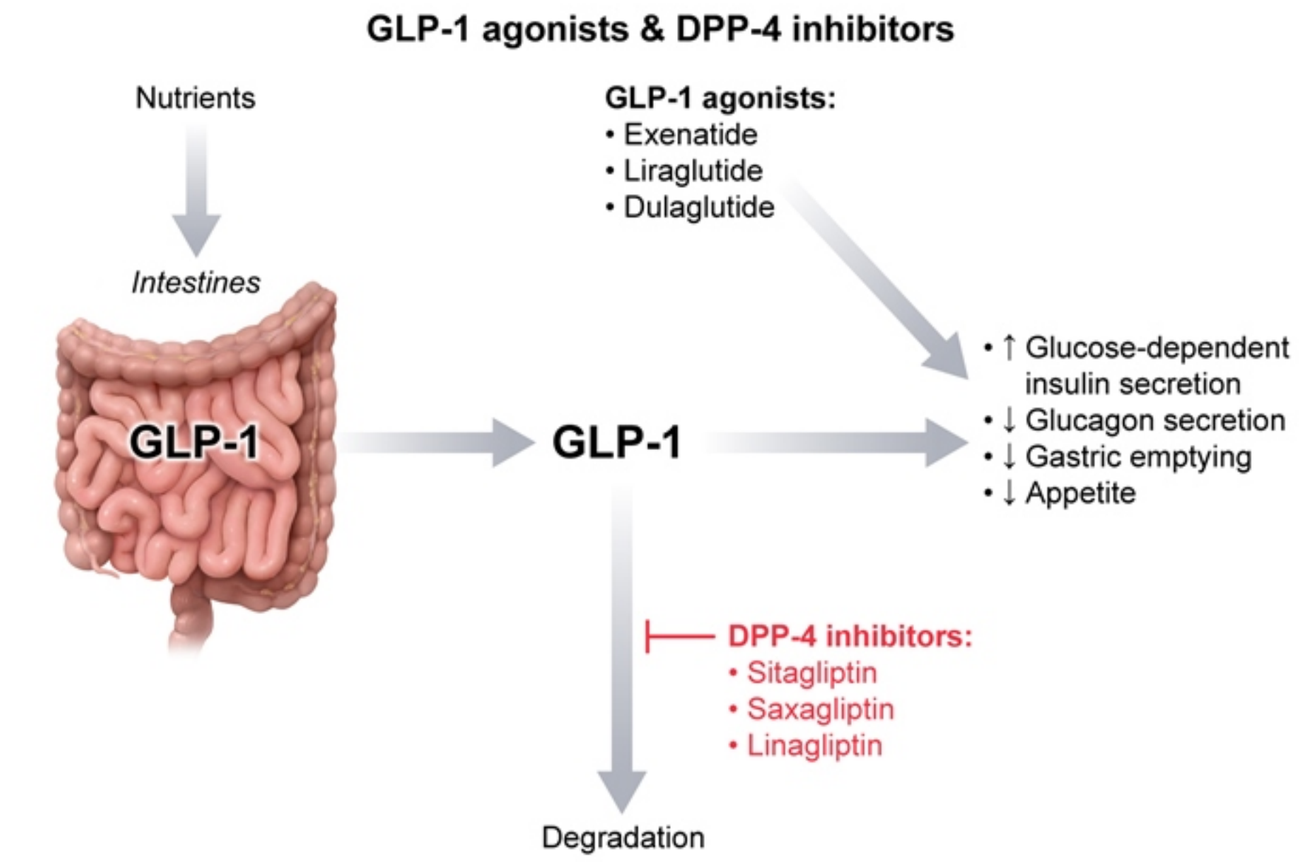

DDP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon like peptide-1.

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Educational objective:

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A 28-year-old woman comes to the office due to progressively worsening eye irritation and double vision over the last 2 months. She also reports unintentional weight loss, mood swings, and palpitations. The patient has no prior medical problems and takes no medications. She has no known drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/70 mm Hg, and pulse is 110/min and regular. Physical examination shows bilateral conjunctival redness and severe proptosis. Appropriate therapy is begun. On a follow-up visit 4 weeks later, her eye symptoms have improved, and examination reveals a small decrease in proptosis with no redness. The drug that improved her ocular symptoms most likely did so by affecting which of the following?

A. Inflammatory infiltration

B. Iodine organification

C. Iodine uptake by the thyroid

D. Sympathetic hyperactivity

E. T3/T4 release by the thyroid

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- ✓ A. Inflammatory infiltration (48%)
- B. Iodine organification (29%)
- C. Iodine uptake by the thyroid (3%)
- D. Sympathetic hyperactivity (8%)
- E. T3/T4 release by the thyroid (9%)

Omitted
Correct answer
A

48%
Answered correctly

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03/28/2020
Last Updated

Explanation

Pathogenesis of Graves ophthalmopathy

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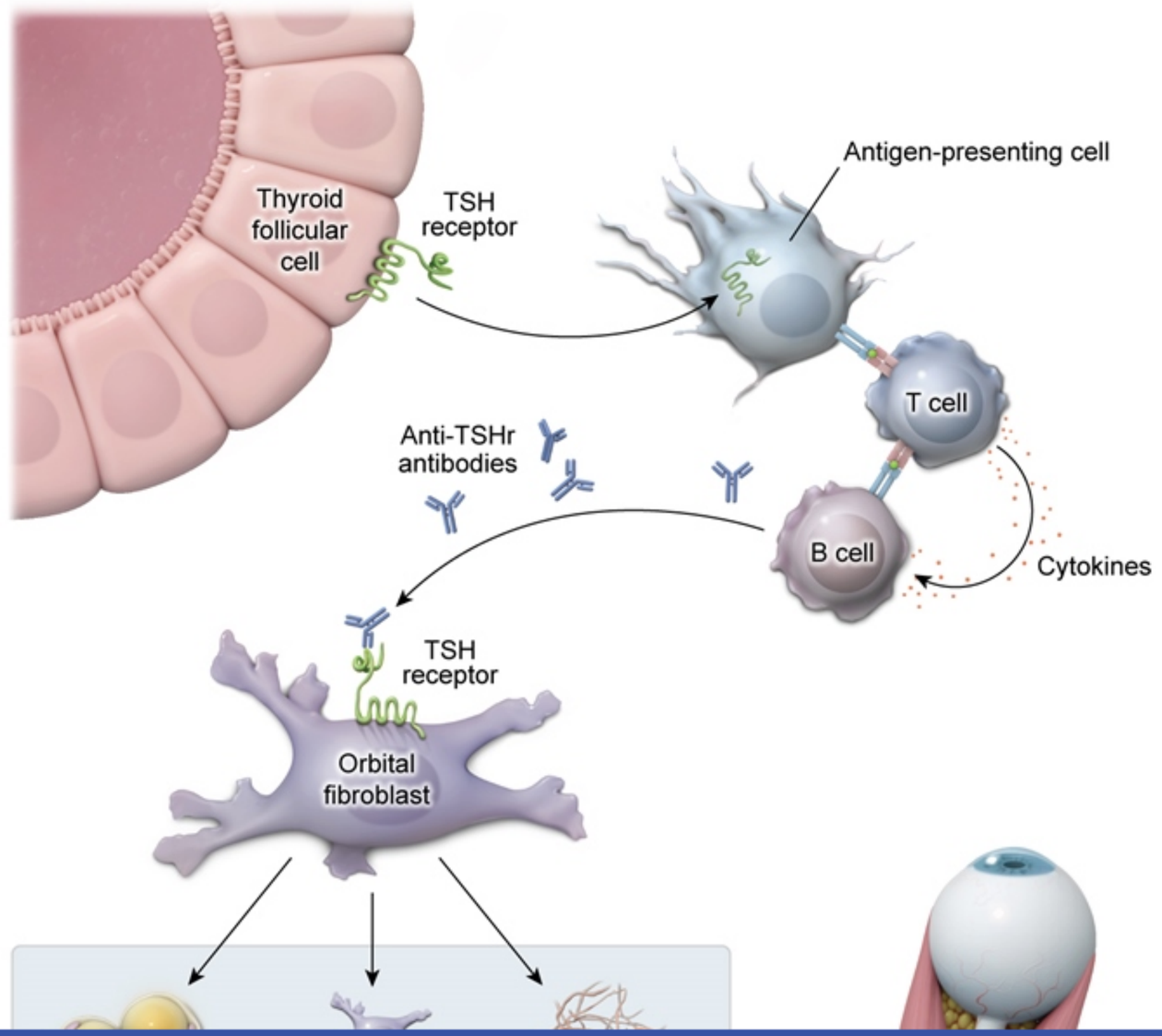
Pathogenesis of Graves ophthalmopathy



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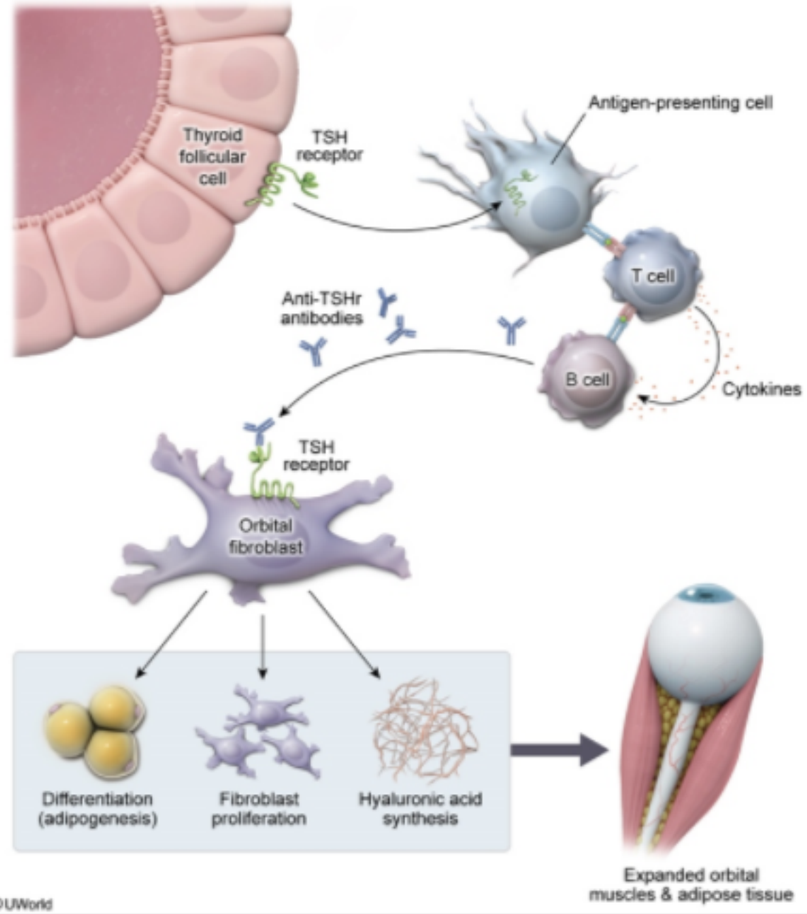
Pathogenesis of Graves ophthalmopathy



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This patient has **Graves disease** with hyperthyroidism (weight loss, palpitations, tachycardia) and significant ophthalmopathy (proptosis, diplopia). Graves disease is an autoimmune disorder triggered by **thyrotropin receptor antibodies**, which bind and activate the TSH receptor. In addition to the thyroid, the TSH receptor is present on fibroblasts, adipocytes, and other cell types. **Graves ophthalmopathy** is caused by stimulation of orbital fibroblasts by thyrotropin receptor antibodies, which leads to excess deposition of extracellular glycosaminoglycans; this is accompanied by T-cell activation and **inflammatory infiltration**. The resultant expansion of extraocular muscles and retro-orbital tissues with the orbit displaces the globe forward, and dysfunction of the extraocular muscles causes restricted extraocular movements and diplopia.

Glucocorticoids (eg, prednisone) decrease peripheral conversion of T4 to T3, but it is their **anti-inflammatory** effects that improve Graves ophthalmopathy. Glucocorticoids decrease the severity of inflammation and reduce the excess extraocular volume. They also can prevent worsening of ophthalmopathy induced by radioactive iodine treatment.

(Choices B, C, and E) Antithyroid drugs (eg, methimazole, propylthiouracil) inhibit thyroid peroxidase, leading to decreased iodine organification and coupling of iodotyrosines. Certain oxoanions (eg, perchlorate, pertechnetate) inhibit the sodium-iodide symporter and reduce iodine uptake by the thyroid. These agents ultimately lead to reduced production and release of thyroid hormone but do not alter the inflammatory process in Graves ophthalmopathy.

(Choice D) Sympathetic activation secondary to hyperthyroidism is responsible for a number of symptoms, including palpitations and tremors. Beta blockers can provide rapid symptomatic relief while awaiting definitive therapy. Although lid lag (which is seen in hyperthyroidism of any cause) would improve with beta blockers, the specific features of Graves ophthalmopathy (eg, diplopia, proptosis) would not be affected.

Educational objective:
Graves ophthalmopathy is caused by stimulation of orbital fibroblasts by thyrotropin receptor antibodies and cytokines released by activated T-cells. Excess deposition of extracellular glycosaminoglycans and inflammatory infiltration lead to expansion of extraocular muscles and retro-orbital tissues. Glucocorticoids improve Graves ophthalmopathy by decreasing the severity of inflammation and reducing the excess extraocular volume.

References

- Glucocorticoid regimens for prevention of Graves' ophthalmopathy progression following radioiodine treatment: systematic review and meta-analysis.

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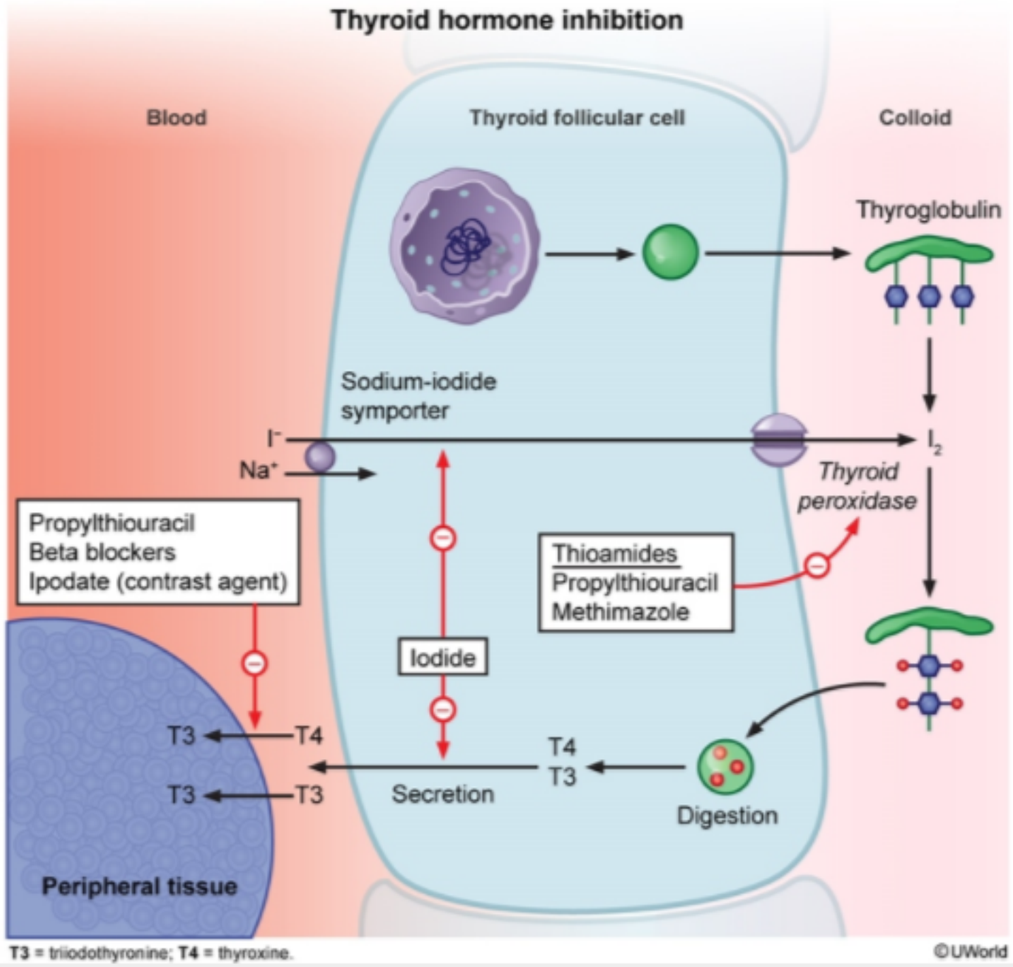

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Educational objective:
Graves ophthalmopathy is caused by stimulation of orbital fibroblasts by thyrotropin receptor antibodies and cytokines released by activated T-cells. Excess deposition of extracellular glycosaminoglycans and inflammatory infiltration lead to expansion of extraocular muscles and retro-orbital tissues. Glucocorticoids improve Graves ophthalmopathy by decreasing the severity of inflammation and reducing the excess extraocular volume.

References

- Glucocorticoid regimens for prevention of Graves' ophthalmopathy progression following radioiodine treatment: systematic review and meta-analysis.

Pharmacology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

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A 52-year-old, post-menopausal woman comes to the office for a follow-up appointment. Six months ago, the patient was evaluated for recurrent, brief episodes of excessive warmth and sweating, which were interfering with her usual activities. Thyroid hormone levels were normal, and the patient was subsequently diagnosed with menopausal hot flashes. Treatment with estrogen-containing hormone replacement therapy was begun with significant symptom improvement. She has no other medical conditions and takes no other medications. Which of the following most likely occurred in this patient as a result of her medication use?

A. Decreased conversion of T4 to T3

B. Decreased thyroid iodine uptake

C. Decreased TSH level

D. Increased free T3 level

E. Increased total T4 level

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A. Decreased conversion of T4 to T3 (18%)

B. Decreased thyroid iodine uptake (3%)

C. Decreased TSH level (31%)

D. Increased free T3 level (6%)

✓ E. Increased total T4 level (39%)

Omitted
Correct answer
E

39%
Answered correctly

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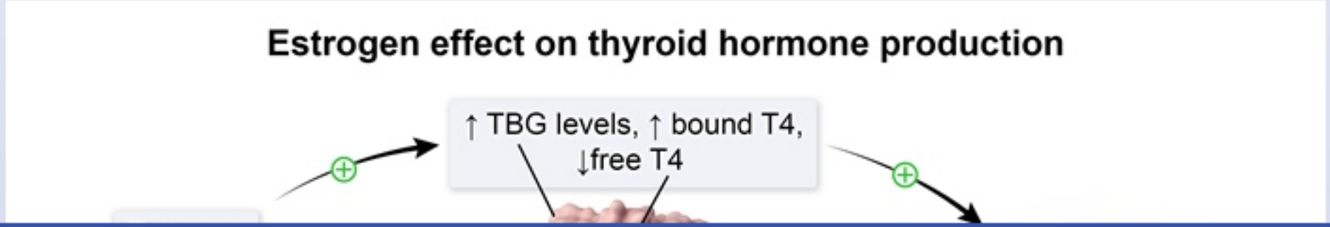
03/31/2020
Last Updated

Explanation



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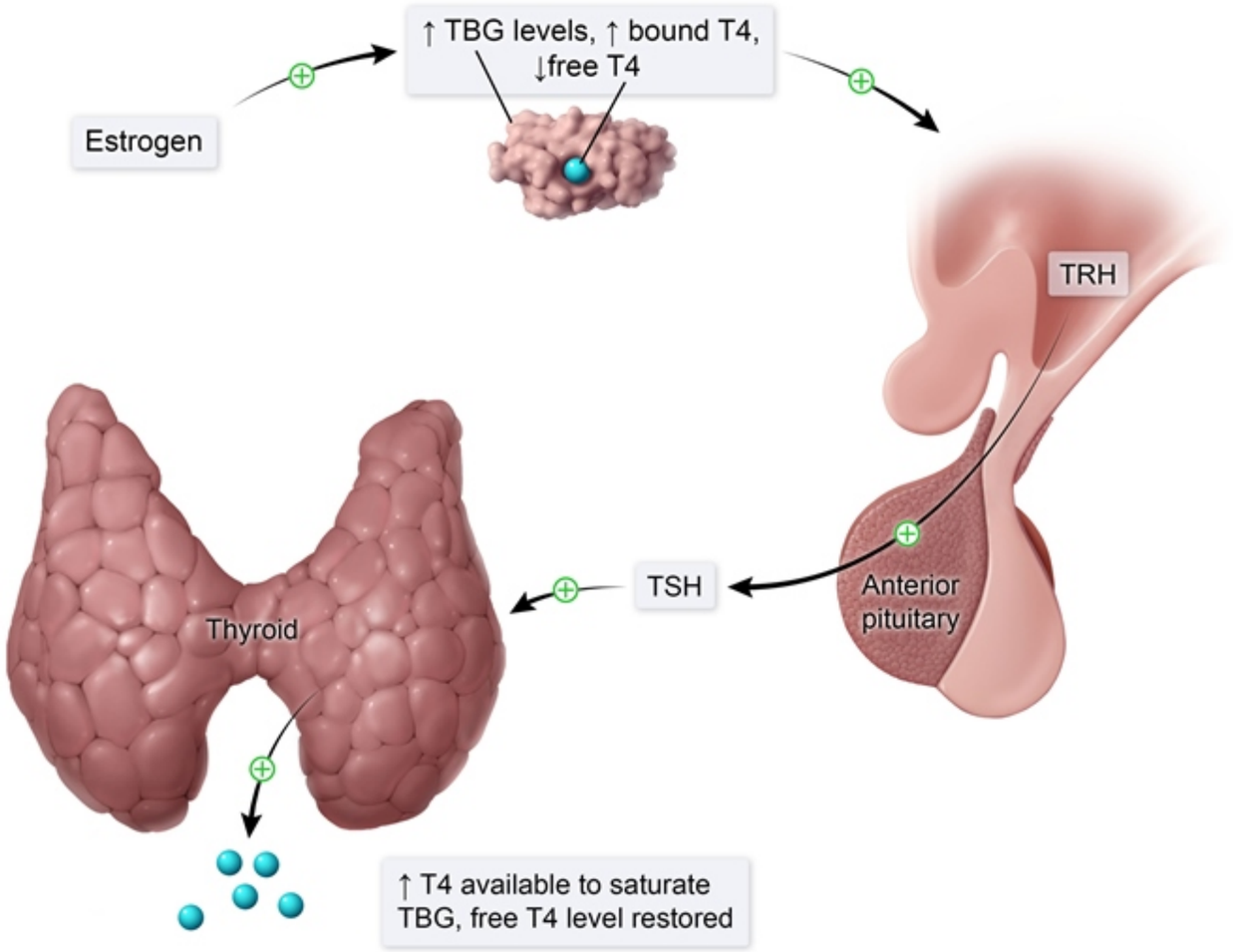
Estrogen effect on thyroid hormone production



TBG = thyroxine-binding globulin.

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Circulating thyroid hormone consists of 2 fractions: an inert **protein-bound** fraction and a **free fraction** that is available to enter target cells via a

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Circulating thyroid hormone consists of 2 fractions: an inert **protein-bound** fraction and a **free fraction** that is available to enter target cells via a carrier-mediated mechanism. More than 99% of circulating thyroid hormone is bound to plasma proteins, creating a large circulating reservoir of thyroid hormone. **Thyroxine-binding globulin** (TBG) accounts for approximately 70% of thyroid hormone binding with an additional share bound by albumin and transthyretin.

An **increase in estrogen activity** (eg, pregnancy, oral contraceptive use, postmenopausal hormone replacement therapy) **raises circulating TBG levels**, causing a corresponding reduction in free T4 and T3 levels. In patients with a normal hypothalamic-pituitary-thyroid axis, this reduction will result in a transient increase in TSH, leading to increased thyroid hormone production until the additional TBG becomes saturated with thyroid hormone and free T4 and T3 levels are restored (ie, patients remain **euthyroid**). Therefore, an increase in the TBG level leads to an **increase in total T4** and T3 (bound plus free fractions).

(Choice A) Estrogen does not affect the peripheral conversion of T4 to T3. Medications that decrease the peripheral conversion of T4 to T3 include propylthiouracil, glucocorticoids, and nonselective beta blockers.

(Choices B and C) Thyroid iodine uptake *increases* transiently due to the temporary *rise* in TSH that occurs with increased TBG synthesis. However, iodine uptake normalizes once the newly synthesized TBG becomes saturated with thyroid hormone and TSH returns to normal.

(Choice D) Increased circulating TBG levels cause a transient *drop* in free T4 and T3 levels as the existing pool of thyroid hormone becomes more protein-bound. However, free T4 and T3 levels quickly normalize as the thyroid synthesizes an appropriate quantity of new thyroid hormone to saturate the additional TBG.

Educational objective:
An increase in estrogen activity, as seen in pregnancy or postmenopausal estrogen replacement therapy, increases the level of thyroxine-binding globulin. This leads to an increase in total thyroid hormone levels, but feedback control maintains normal levels of free (biologically active) thyroid hormone.

Pharmacology	Endocrine, Diabetes & Metabolism	Menopause
Subject	System	Topic

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A 76-year-old woman with type 2 diabetes mellitus is brought to the hospital after her family found her unresponsive in the morning. Her daughter reports that they were busy the previous day with many activities that required extensive walking. The patient ate less dinner than usual because she felt tired. She has discontinued several antidiabetic medications in the past due to medication intolerance but recently has had good glycemic control with a single medication. Blood pressure is 140/80 mm Hg and pulse is 102/min. The patient is diaphoretic and responds only to pain. Pupils are equal, round, and reactive to light. Cardiopulmonary examination is normal. Blood glucose is 34 mg/dL. The patient's condition rapidly improves after administration of an intravenous bolus of dextrose, but she becomes confused again several hours later. Repeat blood glucose is 39 mg/dL. Which of the following medications is the most likely cause of this patient's current condition?

A. Acarbose
B. Glyburide
C. Metformin
D. Pioglitazone
E. Repaglinide
F. Sitagliptin

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- A. Acarbose (4%)
- ✓ B. Glyburide (55%)
- C. Metformin (11%)
- D. Pioglitazone (9%)
- E. Repaglinide (12%)
- F. Sitagliptin (6%)

Omitted
Correct answer
B

55%
Answered correctly

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Time Spent

04/11/2020
Last Updated

Explanation

Noninsulin antidiabetic agents for type 2 diabetes mellitus

Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	**Mechanism of action**	**Side effects**
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
Biguanides • Metformin	Stimulate AMPK & inhibit mitochondrial gluconeogenesis, ↓ hepatic glucose production & ↑ peripheral glucose uptake	• Diarrhea • Lactic acidosis
Thiazolidinediones • Pioglitazone	Activate transcription regulator PPAR-γ, ↓ insulin resistance	• Fluid retention/heart failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
α-glucosidase inhibitors • Acarbose • Miglitol	↓ Intestinal disaccharide absorption	• Diarrhea • Flatulence
SGLT2 inhibitors • Canagliflozin	↑ Renal glucose excretion	• Urinary tract infections

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DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
α-glucosidase inhibitors • Acarbose • Miglitol	↓ Intestinal disaccharide absorption	• Diarrhea • Flatulence
SGLT2 inhibitors • Canagliflozin • Dapagliflozin	↑ Renal glucose excretion	• Urinary tract infections • Hypotension
AMPK = adenosine monophosphate–activated protein kinase; **DPP4** = dipeptidyl peptidase-4; **GIP** = gastric inhibitory polypeptide; **GLP-1** = glucagonlike peptide-1; **K_{ATP}** = ATP-sensitive potassium; **PPAR-γ** = peroxisome proliferator–activated receptor γ; **SGLT2** = sodium-glucose cotransporter 2.		

This patient's **persistent hypoglycemia** is most likely due to an **excessive insulin response** from her diabetes medication. Given the availabile answer options, she was most likely taking a **sulfonylurea** (eg, glyburide).

Sulfonylurea bind to a receptor on pancreatic beta cells and inhibit the ATP-sensitive potassium channel. This alters the cell's resting potential and allows calcium influx, leading to exocytosis of insulin. The net result is increased insulin secretion **independent of blood glucose** concentrations, which confers a significant risk of hypoglycemia.

Hypoglycemia with sulfonylureas can be induced by exercise, missed meals, acute illness, or initiation of additional antidiabetic medications. The risk is greater in the elderly and in patients with metabolic dysfunction (eg, chronic kidney disease, hepatic impairment). As in this patient, sulfonylurea-induced hypoglycemia may reoccur, even after successful initial treatment, until the drug has been cleared from the circulation.

(Choice A) Acarbose is an alpha-glucosidase inhibitor that decreases intestinal glucose absorption and blunts the postprandial rise in serum

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(Choice A) Acarbose is an alpha-glucosidase inhibitor that decreases intestinal glucose absorption and blunts the postprandial rise in serum glucose. Although it can increase insulin sensitivity in the elderly, acarbose is not associated with significant hypoglycemia.

(Choice C) Metformin is a biguanide that decreases hepatic glucose production and intestinal glucose absorption and increases peripheral glucose uptake and utilization. Metformin has rarely been associated with lactic acidosis but does not typically cause hypoglycemia.

(Choice D) Thiazolidinediones (eg, pioglitazone) increase insulin sensitivity by increasing glucose utilization and decreasing glucose production in adipose tissue, muscle, and liver. Thiazolidinediones have been associated with cardiac side effects (eg, heart failure) but carry a low risk of hypoglycemia.

(Choice E) Meglitinides (eg, repaglinide) are insulin secretagogues that induce pancreatic insulin secretion even when blood glucose levels are normal. Although they can cause hypoglycemia, they have a very short half-life (~1 hr) and are less likely than sulfonylureas to cause *prolonged* hypoglycemia, as in this patient.

(Choice F) Sitagliptin is a dipeptidyl peptidase 4 inhibitor that increases *glucose-dependent* insulin release from the pancreatic beta cells. Its effect on insulin release diminishes as glucose levels approach normal, and so it does not usually cause hypoglycemia.

Educational objective:
Sulfonylureas (eg, glyburide, glimepiride) increase insulin secretion by pancreatic beta cells independent of blood glucose concentration. These medications have a high incidence of hypoglycemia, especially in the elderly.

References

- Minimizing hypoglycemia in diabetes.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 46-year-old woman comes to the office due to episodes of headaches, nausea, sweating, and feeling like she is going to pass out. The patient has had 3 such episodes in the past 2 weeks, with symptoms occurring when she skips a meal. During the most recent episode, her fingerstick glucose was 50 mg/dL. She was diagnosed with type 2 diabetes mellitus 3 years ago and was initially treated with metformin monotherapy; glyburide was added to her regimen 3 months ago due to inadequate glycemic control. The patient has no other medical conditions. Vital signs are within normal limits, and physical examination shows no abnormalities. Laboratory results show hemoglobin A1c is 6.7%. The medication most likely causing this patient's current symptoms works by targeting which of the following?

A. Intracellular mitochondrial enzymes

B. Intracellular nuclear receptors

C. Membrane ion channels

D. Surface adenylate cyclase–coupled receptors

E. Surface membrane-bound enzymes

F. Surface tyrosine kinase receptor

Submit

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- A. Intracellular mitochondrial enzymes (2%)
- B. Intracellular nuclear receptors (4%)
- ✓ C. Membrane ion channels (74%)
- D. Surface adenylate cyclase–coupled receptors (5%)
- E. Surface membrane-bound enzymes (2%)
- F. Surface tyrosine kinase receptor (10%)

Omitted
Correct answer
C

74%
Answered correctly

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Time Spent

04/28/2020
Last Updated

Explanation

Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	Mechanism of action	Side effects

Nonhinsulin antidiabetic agents for type 2 diabetes mellitus

Agent	Mechanism of action	Side effects
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
Biguanides • Metformin	Stimulate AMPK & inhibit mitochondrial gluconeogenesis, ↓ hepatic glucose production & ↑ peripheral glucose uptake	• Diarrhea • Lactic acidosis
Thiazolidinediones • Pioglitazone	Activate transcription regulator PPAR-γ, ↓ insulin resistance	• Fluid retention/heart failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
α-glucosidase inhibitors • Acarbose • Miglitol	↓ Intestinal disaccharide absorption	• Diarrhea • Flatulence
SGLT2 inhibitors • Canagliflozin • Dapagliflozin	↑ Renal glucose excretion	• Urinary tract infections • Hypotension

DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
α-glucosidase inhibitors • Acarbose • Miglitol	↓ Intestinal disaccharide absorption	• Diarrhea • Flatulence
SGLT2 inhibitors • Canagliflozin • Dapagliflozin	↑ Renal glucose excretion	• Urinary tract infections • Hypotension
AMPK = adenosine monophosphate–activated protein kinase; **DPP4** = dipeptidyl peptidase-4; **GIP** = gastric inhibitory polypeptide; **GLP-1** = glucagonlike peptide-1; **K_{ATP}** = ATP-sensitive potassium; **PPAR-γ** = peroxisome proliferator–activated receptor γ; **SGLT2** = sodium-glucose cotransporter 2.		

This patient has symptomatic hypoglycemia following initiation of a sulfonylurea medication (ie, glyburide) for diabetes mellitus. **Sulfonylureas** inhibit the **ATP-sensitive potassium channel** on the pancreatic beta **cell membrane**, inducing depolarization and L-type calcium channel opening. The increased Ca^{2+} influx stimulates beta cell **insulin release** independent of blood glucose concentrations.

Sulfonylureas continue to stimulate insulin secretion even when blood glucose levels are normal, which can lead to hypoglycemia. The longer-acting sulfonylureas (eg, glyburide) are more prone to causing **hypoglycemia** than shorter-acting drugs (eg, glipizide). Meglitinides (eg, repaglinide, nateglinide) are short-acting drugs that are functionally similar to sulfonylureas.

(Choice A) Metformin inhibits the mitochondrial enzymes required for gluconeogenesis, leading to decreased hepatic glucose production and lower circulating glucose levels. It also increases peripheral glucose uptake and improves insulin sensitivity by activating AMP-activated protein kinase. Metformin does not increase endogenous insulin secretion and is therefore less likely to cause hypoglycemia than sulfonylureas.

(Choice B) Thiazolidinediones (eg, pioglitazone) decrease insulin resistance by binding to peroxisome proliferator–activated receptor gamma, a transcriptional regulator of genes involved in glucose and lipid metabolism.

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repaglinide, nateglinide) are short-acting drugs that are functionally similar to sulfonylureas.

(Choice A) Metformin inhibits the mitochondrial enzymes required for gluconeogenesis, leading to decreased hepatic glucose production and lower circulating glucose levels. It also increases peripheral glucose uptake and improves insulin sensitivity by activating AMP-activated protein kinase. Metformin does not increase endogenous insulin secretion and is therefore less likely to cause hypoglycemia than sulfonylureas.

(Choice B) Thiazolidinediones (eg, pioglitazone) decrease insulin resistance by binding to peroxisome proliferator–activated receptor gamma, a transcriptional regulator of genes involved in glucose and lipid metabolism.

(Choice D) Glucagon-like polypeptide-1 (GLP-1) is secreted by intestinal L cells in response to food intake, and regulates glucose by slowing gastric emptying and increasing insulin release. GLP-1 (and pharmacologic GLP-1 agonists such as exenatide) acts through cell surface receptors that are coupled with a G protein–adenylyl cyclase system.

(Choice E) Alpha-glucosidase inhibitors (eg, acarbose, miglitol) decrease the activity of disaccharidases on the intestinal brush border. Because carbohydrates are absorbed as monosaccharides, the inhibition of disaccharide breakdown delays carbohydrate absorption.

(Choice F) Insulin acts by binding to a cell surface receptor consisting of 2 alpha and 2 beta subunits. The alpha subunits are located extracellularly and provide binding sites for insulin. The membrane-spanning beta subunits contain the intracellular tyrosine kinase domains.

Educational objective:
Sulfonylureas inhibit the ATP-sensitive potassium channel on the pancreatic beta cell membrane, inducing depolarization and L-type calcium channel opening. The increased Ca^{2+} influx stimulates beta cell insulin release independent of blood glucose concentrations. Sulfonylureas can induce hypoglycemia because they stimulate insulin secretion even when blood glucose levels are normal.

References

- The role of nateglinide and repaglinide, derivatives of meglitinide, in the treatment of type 2 diabetes mellitus.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A nuclear waste disposal plant suffers a containment failure and several grams of iodine-131 are released into the local environment. A number of workers are believed to have been exposed to dangerous levels of the radioactive material. Which of the following should be immediately administered to help prevent tissue damage in these individuals?

A. Levothyroxine

B. Potassium iodide

C. Prednisone

D. Propranolol

E. Propylthiouracil

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A nuclear waste disposal plant suffers a containment failure and several grams of iodine-131 are released into the local environment. A number of workers are believed to have been exposed to dangerous levels of the radioactive material. Which of the following should be immediately administered to help prevent tissue damage in these individuals?

A. Levothyroxine (6%)
✓ B. Potassium iodide (67%)
C. Prednisone (1%)
D. Propranolol (1%)
E. Propylthiouracil (23%)

Omitted
Correct answer
B

67%
Answered correctly

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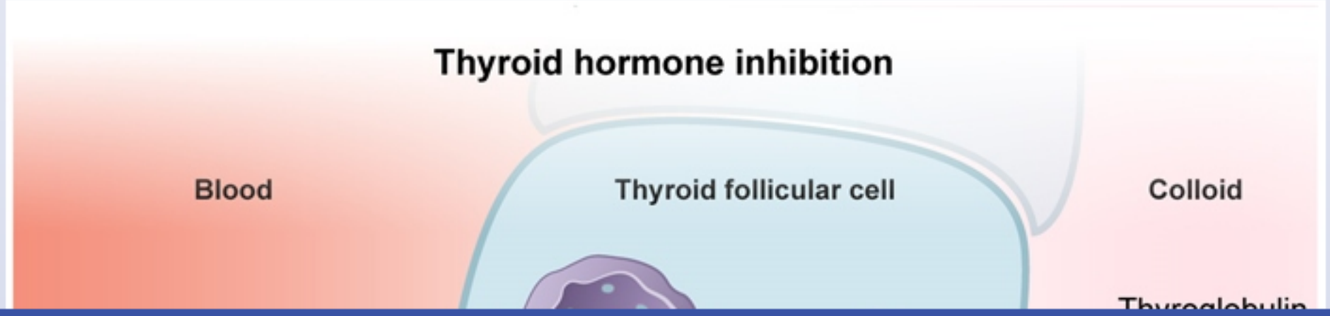
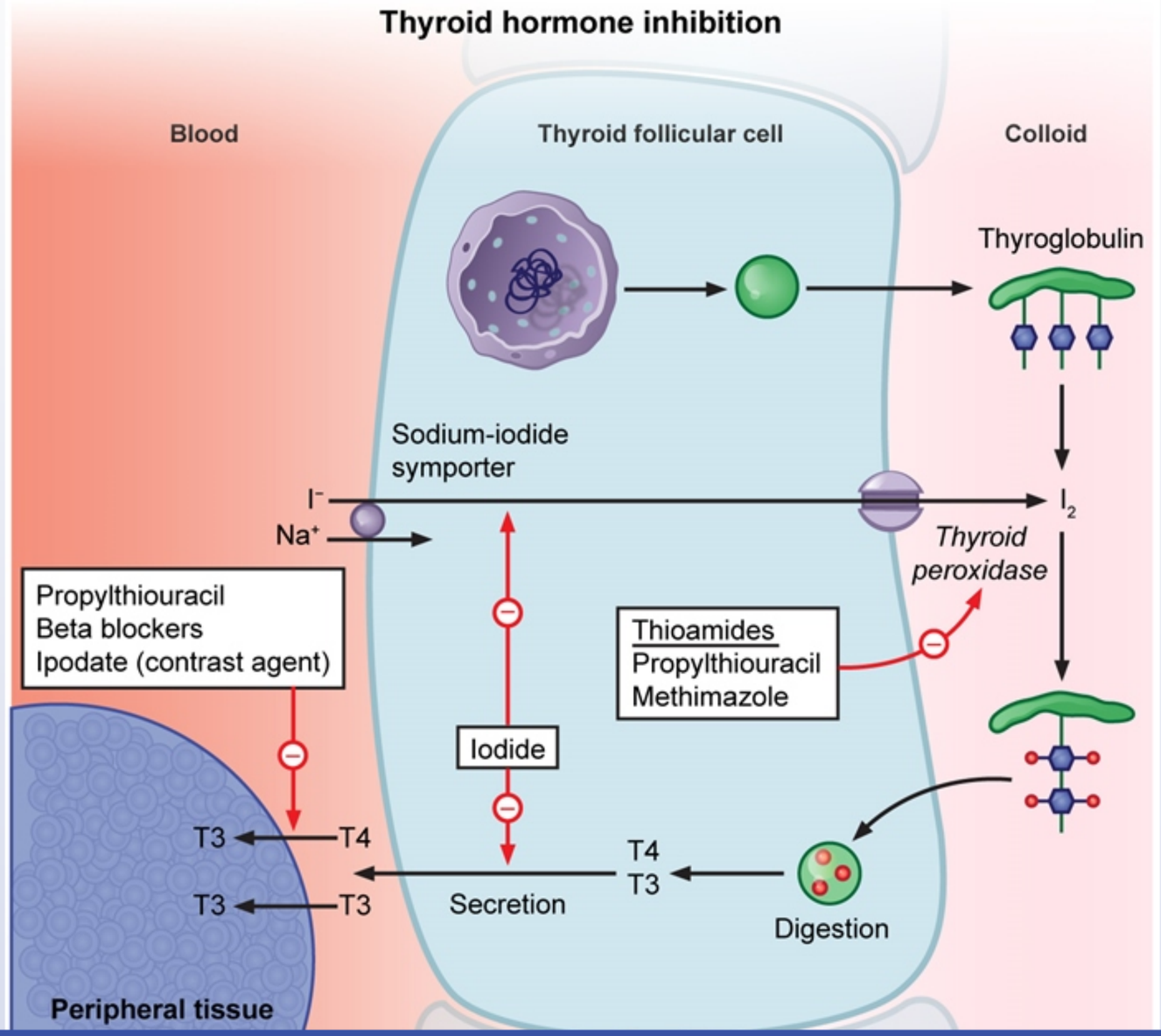
Last Updated

Explanation




Thyroid hormone inhibition
Blood
Thyroid follicular cell
Colloid
Thyroglobulin
Sodium-iodide symporter
I⁻
Na⁺
I₂
Thyroid peroxidase
Propylthiouracil
Beta blockers
Ipodate (contrast agent)
Thioamides
Propylthiouracil
Methimazole
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Digestion
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Radioactive material such as **iodine-131 (^{131}I)** can be released into the environment following nuclear reactor accidents, breach-of-containment at waste disposal sites, or atomic bomb blasts. Like non-radioactive iodine, ^{131}I is preferentially taken up and concentrated within the **thyroid gland**. There it can cause significant tissue damage that may result in radiation-induced hypothyroidism and **thyroid carcinoma** (particularly in younger patients). In the event of a nuclear accident, **potassium iodide** is given prophylactically to protect the thyroid from excessive accumulation of radioactive ^{131}I.

Energy-dependent transport of inorganic iodide into the thyroid follicular cell (iodide trapping) is accomplished by the sodium-iodide symporter located on the basolateral membrane. Because this transporter takes up all isotopes of iodide (as well as other ions such as perchlorate and pertechnetate), high serum levels of nonradioactive iodide can **competitively inhibit** radioactive I^{131} from entering thyroid follicular cells. Large increases in serum iodide levels also inhibit iodine organification (Wolff-Chaikoff effect) and reduce thyroid hormone release.

(Choice A) Levothyroxine is a synthetic form of T4 used to treat hypothyroidism. High doses of levothyroxine suppress TSH, just as high amounts of natural T4 would. Because TSH stimulates iodine trapping, high doses of levothyroxine would ultimately reduce iodine uptake in the thyroid follicular cells. However, this regulatory process requires several days to weeks to take effect.

(Choices C and D) Propranolol is used to reduce the adrenergic effects of thyrotoxicosis (eg, tachycardia, tremor). Prednisone is used to reduce lymphocyte-mediated inflammatory effects in Graves ophthalmopathy. However, neither propranolol nor prednisone affects the uptake of iodine in thyroid follicular cells.

(Choice E) Propylthiouracil is used in the treatment of hyperthyroidism and decreases formation of thyroid hormone by inhibiting the enzyme thyroid peroxidase. Although inhibition of iodine organification will cause decreased iodide uptake by the thyroid, potassium iodide promotes this effect more rapidly and efficiently by also acting as a competitive inhibitor for iodide entry into the cell.

Educational objective:
Potassium iodide competitively inhibits thyroid uptake of radioactive iodine isotopes and is often administered following nuclear accidents to protect the thyroid and prevent development of radiation-induced thyroid carcinoma.

References

- Potassium iodide (KI) to block the thyroid from exposure to I-131: current questions and answers to be discussed.

A 65-year-old man comes to the office due to advanced prostate cancer with bone metastases. For the last 4 months, he has been treated with a GnRH agonist, which has significantly reduced his bone pain. However, the patient now reports discomfort at the anterior chest wall. Physical examination reveals bilateral, mildly tender enlargement of the breast tissue behind the nipple-areolar complex. Which of the following medications, if initiated early, could have most effectively prevented this patient's breast symptoms?

A. Bicalutamide

B. Danazol

C. Finasteride

D. Spironolactone

E. Tamoxifen

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A. Bicalutamide (6%)
B. Danazol (16%)
C. Finasteride (17%)
D. Spironolactone (9%)
✓ E. Tamoxifen (50%)

Omitted
Correct answer
E

50%
Answered correctly

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01/23/2020
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Explanation

Gynecomastia	
Clinical findings	• Development of glandular breast tissue in males
Pathophysiology	• Increased estrogen/androgen ratio • Ductal epithelial hyperplasia & stromal fibrosis

Gynecomastia	
Clinical findings	• Development of glandular breast tissue in males
Pathophysiology	• Increased estrogen/androgen ratio • Ductal epithelial hyperplasia & stromal fibrosis

Common etiologies	• Increased estrogen levels (eg, cirrhosis, obesity)
	• Decreased testosterone levels (eg, chronic kidney disease, hypogonadism)
	• Medication effect
	  ∘ Decreased androgen production (eg, GnRH agonists, ketoconazole)
	  ∘ Decreased conversion to dihydrotestosterone (eg, 5-alpha reductase inhibitors)
	  ∘ Inhibition of androgen receptors (eg, spironolactone, bicalutamide)

Gynecomastia is the development of glandular breast tissue in males. It is characterized by ductal epithelial hyperplasia with fibrosis of the surrounding stroma. Breast growth is inhibited by androgens and promoted by estrogens; conditions that increase the **estrogen to androgen ratio** can lead to gynecomastia. Common pathologic causes include cirrhosis (increased aromatase activity, decreased clearance of estrogens), end-stage renal disease (decreased testosterone production), and medications (eg, spironolactone, ketoconazole).

Men with prostate cancer who receive **androgen-deprivation therapy** (eg, orchiectomy, long-acting GnRH agonists, androgen receptor inhibitors) can develop gynecomastia due to dramatic (>95%) reductions in circulating testosterone (with lesser reductions in estrogens). Treatment with **tamoxifen**, a selective estrogen receptor modulator that acts as an estrogen antagonist in the breast, can reduce the risk of gynecomastia in these patients.

(Choice A) Bicalutamide is a testosterone receptor antagonist used in the treatment of prostate cancer. This drug can cause or worsen gynecomastia due to the reduced physiologic testosterone effect.

(Choice B) Danazol is a synthetic steroid with androgenic and antiestrogenic effects. It may improve gynecomastia in patients with hypogonadism but can lead to rapid growth of prostate cancer and would not be appropriate for this patient.

(Choices C and D) Finasteride is a 5-α reductase inhibitor that reduces the conversion of testosterone to dihydrotestosterone; it is used for

- Decreased conversion to dihydrotestosterone (eg, 5-alpha reductase inhibitors)

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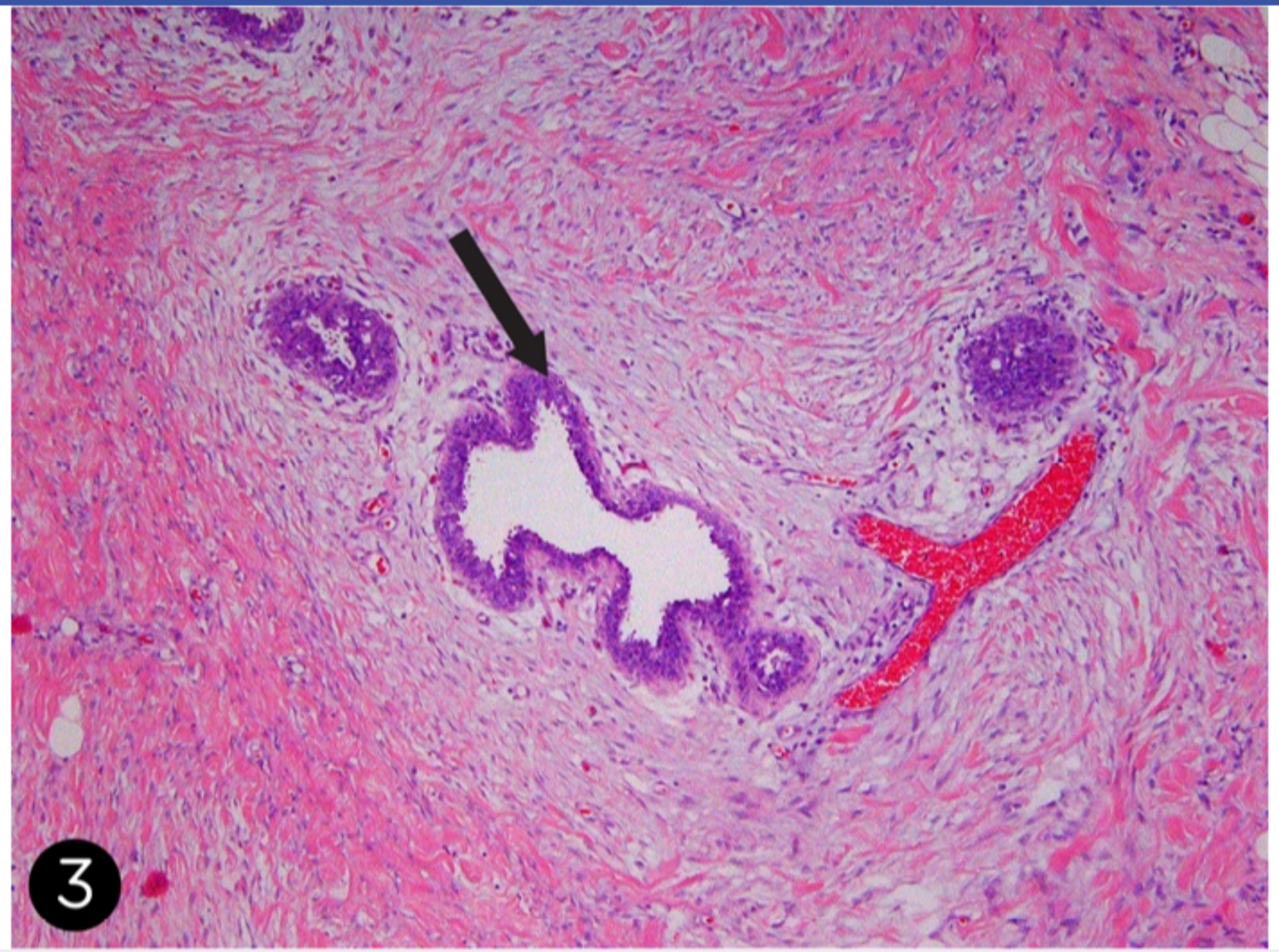

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(Choices C and D) Finasteride is a 5-α reductase inhibitor that reduces the conversion of testosterone to dihydrotestosterone; it is used for treatment of benign prostatic hyperplasia and male-pattern hair loss. Spironolactone is an aldosterone antagonist that also decreases testosterone production and inhibits the testosterone receptor; it is commonly used for heart failure, cirrhosis, and hypertension. Both of these agents are associated with increased risk of gynecomastia.

Educational objective:
Gynecomastia is the development of glandular breast tissue in males and is commonly seen in men receiving androgen deprivation therapy for prostate cancer. Tamoxifen inhibits the effect of estrogen on breast tissue and can reduce the risk of gynecomastia in these patients.

References

- Treatment of gynecomastia in patients with prostate cancer and androgen deprivation.

Pharmacology	Endocrine, Diabetes & Metabolism	Gynecomastia
Subject	System	Topic

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A 64-year-old woman is brought to the emergency department due to confusion and lethargy. The patient was asymptomatic when her husband left for work in the morning, but when he arrived home, he found her in bed weak and disoriented. The patient's medical conditions include type 2 diabetes mellitus and hypertension, for which she takes multiple medications. She does not use tobacco, alcohol, or illicit drugs. Temperature is 37 C (98.6 F), blood pressure is 140/70 mm Hg, pulse is 74/min, and respirations are 18/min. On physical examination, the patient is somnolent but withdraws all extremities to pain. Laboratory testing shows an elevated serum C-peptide level. If her current condition is due to an antidiabetic drug, which of the following is the most likely culprit agent?

- A. Acarbose
- B. Canagliflozin
- C. Glyburide
- D. Long-acting insulin
- E. Metformin
- F. Pioglitazone
- G. Short-acting insulin

Submit

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- A. Acarbose (1%)
- B. Canagliflozin (2%)
- ✓ C. Glyburide (73%)
- D. Long-acting insulin (4%)
- E. Metformin (6%)
- F. Pioglitazone (6%)
- G. Short-acting insulin (5%)

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Correct answer
C

73%
Answered correctly

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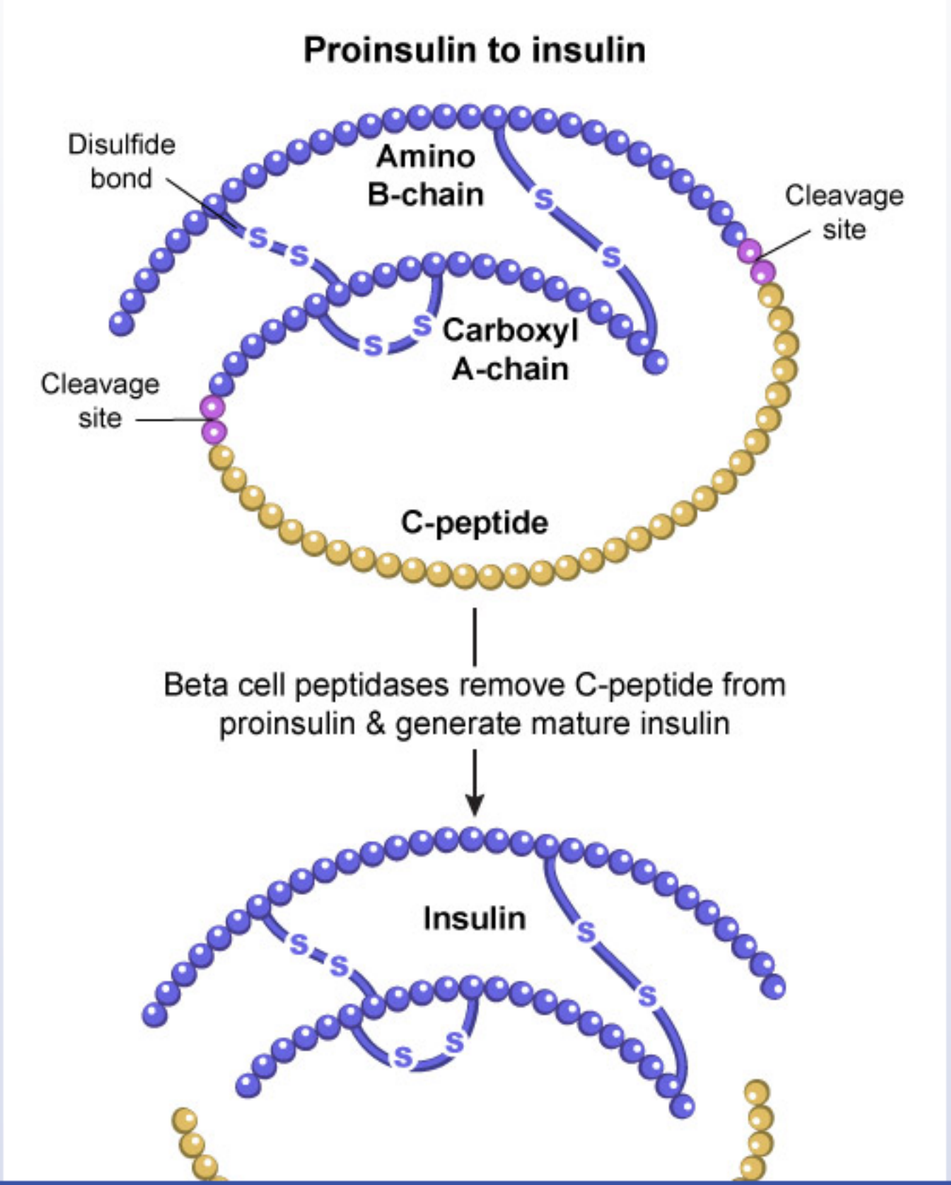
Explanation

Proinsulin to insulin


Proinsulin to insulin
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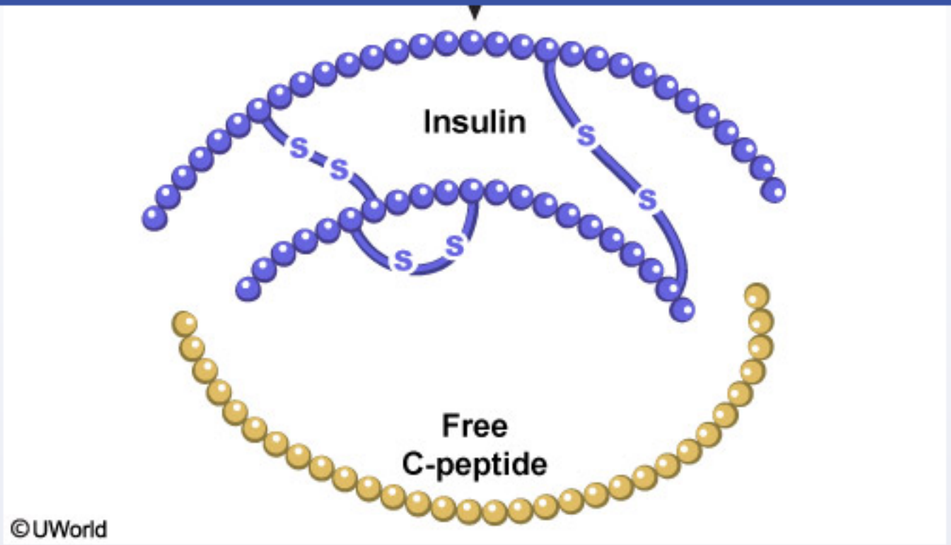
Insulin



This patient with type 2 diabetes mellitus has acute confusion and lethargy, which is consistent with symptomatic **hypoglycemia**, a common adverse effect of antidiabetic medications. Her **elevated C-peptide** level is further indicative of a medication that stimulates pancreatic insulin secretion independent of blood glucose levels, such as **sulfonylureas** (eg, glyburide) or meglitinides.

Insulin is synthesized in pancreatic beta cells as preproinsulin, which is guided by a signal peptide into the rough endoplasmic reticulum during translation. The signal peptide is then removed, converting preproinsulin to proinsulin. Protein folding and disulfide bond formation take place as proinsulin traverses the rough endoplasmic reticulum. Proinsulin is then transported to the Golgi apparatus, where it is packaged with proteolytic enzymes into insulin secretory granules and cleaved into mature insulin and C-peptide. **C-peptide and insulin** are then **co-secreted** from pancreatic beta cells in equimolar amounts.

When hypoglycemia is due to **excessive endogenous insulin** production (eg, sulfonylureas, meglitinides, insulinoma), C-peptide levels are elevated. In contrast, exogenous insulin and insulin analogs (ie, insulin-like polypeptides with alterations in the amino acid sequence to optimize pharmacokinetic properties) do not contain C-peptide. When hypoglycemia is induced by these agents, endogenous insulin secretion is suppressed and C-peptide levels are low **(Choices D and G)**.

(Choice A) Acarbose inhibits alpha-glucosidase in the intestinal brush border, impairing the hydrolysis of polymeric carbohydrates and leading to decreased postprandial glucose absorption. Acarbose indirectly *decreases* endogenous insulin (and C-peptide) secretion by reducing

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References

Noninsulin antidiabetic agents for type 2 diabetes mellitus

Agent	Mechanism of action	Side effects
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
Biguanides • Metformin	Stimulate AMPK & inhibit mitochondrial gluconeogenesis, ↓ hepatic glucose production & ↑ peripheral glucose uptake	• Diarrhea • Lactic acidosis
Thiazolidinediones • Pioglitazone	Activate transcription regulator PPAR-γ, ↓ insulin resistance	• Fluid retention/heart failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
α-glucosidase inhibitors • Acarbose • Miglitol	↓ Intestinal disaccharide absorption	• Diarrhea • Flatulence
SGLT2 inhibitors • Canagliflozin • Dapagliflozin	↑ Renal glucose excretion	• Urinary tract infections • Hypotension

AMPK = adenosine monophosphate–activated protein kinase; **DPP4** = dipeptidyl peptidase-4; **GIP** = gastric inhibitory polypeptide; **GLP-**

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enzymes into insulin secretory granules and cleaved into mature insulin and C-peptide. **C-peptide and insulin** are then **co-secreted** from pancreatic beta cells in equimolar amounts.

When hypoglycemia is due to **excessive endogenous insulin** production (eg, sulfonylureas, meglitinides, insulinoma), C-peptide levels are elevated. In contrast, exogenous insulin and insulin analogs (ie, insulin-like polypeptides with alterations in the amino acid sequence to optimize pharmacokinetic properties) do not contain C-peptide. When hypoglycemia is induced by these agents, endogenous insulin secretion is suppressed and C-peptide levels are low **(Choices D and G)**.

(Choice A) Acarbose inhibits alpha-glucosidase in the intestinal brush border, impairing the hydrolysis of polymeric carbohydrates and leading to decreased postprandial glucose absorption. Acarbose indirectly *decreases* endogenous insulin (and C-peptide) secretion by reducing postprandial hyperglycemia.

(Choices B, E, and F) Sodium-glucose cotransporter-2 inhibitors (eg, canagliflozin, dapagliflozin) act in the kidney to decrease the reabsorption of filtered glucose. Major side effects include hypotension and urinary tract infection. Metformin is a biguanide that decreases hepatic glucose production, decreases intestinal glucose absorption, and increases peripheral glucose uptake and utilization. Thiazolidinediones (eg, pioglitazone) increase insulin sensitivity by increasing glucose utilization and decreasing glucose production in adipose tissue, muscle, and liver. These agents have a *low risk of hypoglycemia* and *do not increase endogenous insulin secretion*.

Educational objective:
Proinsulin is cleaved into mature insulin and C-peptide, which are co-secreted from pancreatic beta cells in equimolar amounts. Circulating levels of C-peptide can be used as a marker of endogenous insulin secretion. Sulfonylureas and meglitinides lower blood glucose by stimulating pancreatic insulin secretion; hypoglycemia due to these agents is associated with elevated C-peptide levels.

References

- Regulation of insulin synthesis and secretion and pancreatic beta-cell dysfunction in diabetes.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 48-year-old woman with a complex medical history comes to the clinic due to a change in her body habitus. She says her legs are "like sticks" while her "belly is getting bigger." The patient also feels increasingly fatigued but does not have excessive daytime somnolence. She has been homeless for much of the last 5 years but has been living in a residential care facility for the last 12 months. On physical examination, she is distractible and has an inappropriate affect but is cooperative. Neurologic and mental status examination is otherwise normal. There is loss of adipose tissue from the extremities and face, with a noticeable increase in abdominal girth. Which of the following types of medications is most likely to be responsible for this patient's symptoms?

A. Antiretroviral medication
B. HMG-CoA reductase inhibitor
C. Loop diuretic
D. Nonsteroidal antiinflammatory drug
E. Proton pump inhibitor
F. Selective serotonin reuptake inhibitor
G. Thyroperoxidase inhibitor

Submit

A 48-year-old woman with a complex medical history comes to the clinic due to a change in her body habitus. She says her legs are "like sticks" while her "belly is getting bigger." The patient also feels increasingly fatigued but does not have excessive daytime somnolence. She has been homeless for much of the last 5 years but has been living in a residential care facility for the last 12 months. On physical examination, she is distractible and has an inappropriate affect but is cooperative. Neurologic and mental status examination is otherwise normal. There is loss of adipose tissue from the extremities and face, with a noticeable increase in abdominal girth. Which of the following types of medications is most likely to be responsible for this patient's symptoms?

- ✓ A. Antiretroviral medication (53%)
- B. HMG-CoA reductase inhibitor (7%)
- C. Loop diuretic (2%)
- D. Nonsteroidal antiinflammatory drug (3%)
- E. Proton pump inhibitor (1%)
- F. Selective serotonin reuptake inhibitor (11%)
- G. Thyroperoxidase inhibitor (20%)

Omitted
Correct answer
A

53%
Answered correctly

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Explanation

This patient has **redistribution of fat** from the extremities to the trunk. Medication-induced body fat redistribution (sometimes called **lipoatrophy**

This patient has **redistribution of fat** from the extremities to the trunk. Medication-induced body fat redistribution (sometimes called **lipoatrophy** or **lipodystrophy**) is a common adverse effect of **highly-active antiretroviral therapy (HAART)** and can be considered a product of 2 independent processes: wasting of fat from the face and extremities and deposition of fat in the trunk and viscera.

1. **Lipoatrophy** refers to loss of subcutaneous fat, especially from the face, extremities, and buttocks. It is primarily seen in patients taking nucleoside reverse transcriptase inhibitors (mainly stavudine and zidovudine) and is also associated with protease inhibitor use.
2. **Central fat deposition** also occurs in some patients and causes increased abdominal girth and a buffalo hump (dorsocervical fat accumulation) that is similar to Cushing syndrome. Central fat deposition may be seen with any HIV treatment regimen and may be a result of treating HIV rather than a specific medication adverse effect.

Both syndromes have been associated with **metabolic abnormalities** including insulin resistance, hypertriglyceridemia, and reduced HDL cholesterol levels.

(Choice B) HMG-CoA reductase inhibitors (statins) are associated with myalgias and an increase in hepatic transaminase levels. They do not cause fat redistribution.

(Choice C) Thiazide diuretics (eg, chlorthalidone, hydrochlorothiazide) can cause hyperglycemia and hypertriglyceridemia and may have a small effect on fat distribution. However, these effects have not been seen with loop diuretics (eg, furosemide).

(Choice D) Unlike glucocorticoids, nonsteroidal antiinflammatory drugs (NSAIDs) do not significantly alter tissue lipid metabolism or cause fat redistribution.

(Choice E) Proton pump inhibitors (PPIs) are used to reduce gastric acid secretion in patients with peptic ulcer and gastroesophageal reflux. PPIs can cause hypomagnesemia and increased risk of osteoporosis.

(Choice F) Selective serotonin reuptake inhibitors are indicated for treatment of depression and chronic anxiety. They can cause weight gain in a subset of patients but have not been linked to fat redistribution.

(Choice G) Thyroperoxidase inhibitors (eg, methimazole, propylthiouracil) are used to treat hyperthyroidism. Common side effects include bone marrow suppression (eg, anemia, agranulocytosis).

Educational objective:

(Choice B) HMG-CoA reductase inhibitors (statins) are associated with myalgias and an increase in hepatic transaminase levels. They do not cause fat redistribution.

(Choice C) Thiazide diuretics (eg, chlorthalidone, hydrochlorothiazide) can cause hyperglycemia and hypertriglyceridemia and may have a small effect on fat distribution. However, these effects have not been seen with loop diuretics (eg, furosemide).

(Choice D) Unlike glucocorticoids, nonsteroidal antiinflammatory drugs (NSAIDs) do not significantly alter tissue lipid metabolism or cause fat redistribution.

(Choice E) Proton pump inhibitors (PPIs) are used to reduce gastric acid secretion in patients with peptic ulcer and gastroesophageal reflux. PPIs can cause hypomagnesemia and increased risk of osteoporosis.

(Choice F) Selective serotonin reuptake inhibitors are indicated for treatment of depression and chronic anxiety. They can cause weight gain in a subset of patients but have not been linked to fat redistribution.

(Choice G) Thyroperoxidase inhibitors (eg, methimazole, propylthiouracil) are used to treat hyperthyroidism. Common side effects include bone marrow suppression (eg, anemia, agranulocytosis).

Educational objective:
Highly-active antiretroviral therapy (HAART) for HIV is commonly associated with body fat redistribution. Subcutaneous lipoatrophy involving the face and extremities is associated with nucleoside reverse transcriptase inhibitors (especially stavudine and zidovudine) and protease inhibitors. Central fat accumulation in the trunk and viscera can occur with any HAART regimen.

References

- Systematic review of antiretroviral-associated lipodystrophy: lipoatrophy, but not central fat gain, is an antiretroviral adverse drug reaction.
- Prevalence of, evolution of, and risk factors for fat atrophy and fat deposition in a cohort of HIV-infected men and women.

Pharmacology	Endocrine, Diabetes & Metabolism	Lipodystrophy
Subject	System	Topic

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A 60-year-old man comes to the office for follow-up of type 2 diabetes mellitus. His current treatment regimen includes metformin and a once-daily injection of a long-acting subcutaneous insulin. The patient is adherent with the treatment and has a healthy lifestyle. Review of his home glucose measurements shows that his postprandial glucose levels are frequently elevated; however, fasting levels are normal. He has no other medical conditions and does not use tobacco, alcohol, or illicit drugs. Vital signs are within normal limits. Physical examination shows no abnormalities. Laboratory testing reveals hemoglobin A1c is 8.3%. Additional insulin therapy 3 times a day before each meal is planned to improve glycemic control. Which of the following types of insulin would be most appropriate for the additional therapy?

A. Insulin aspart
B. Insulin degludec
C. Insulin detemir
D. Insulin glargine
E. NPH insulin

Submit

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- ✓ A. Insulin aspart (77%)
- B. Insulin degludec (1%)
- C. Insulin detemir (3%)
- D. Insulin glargine (9%)
- E. NPH insulin (8%)

Omitted
Correct answer
A

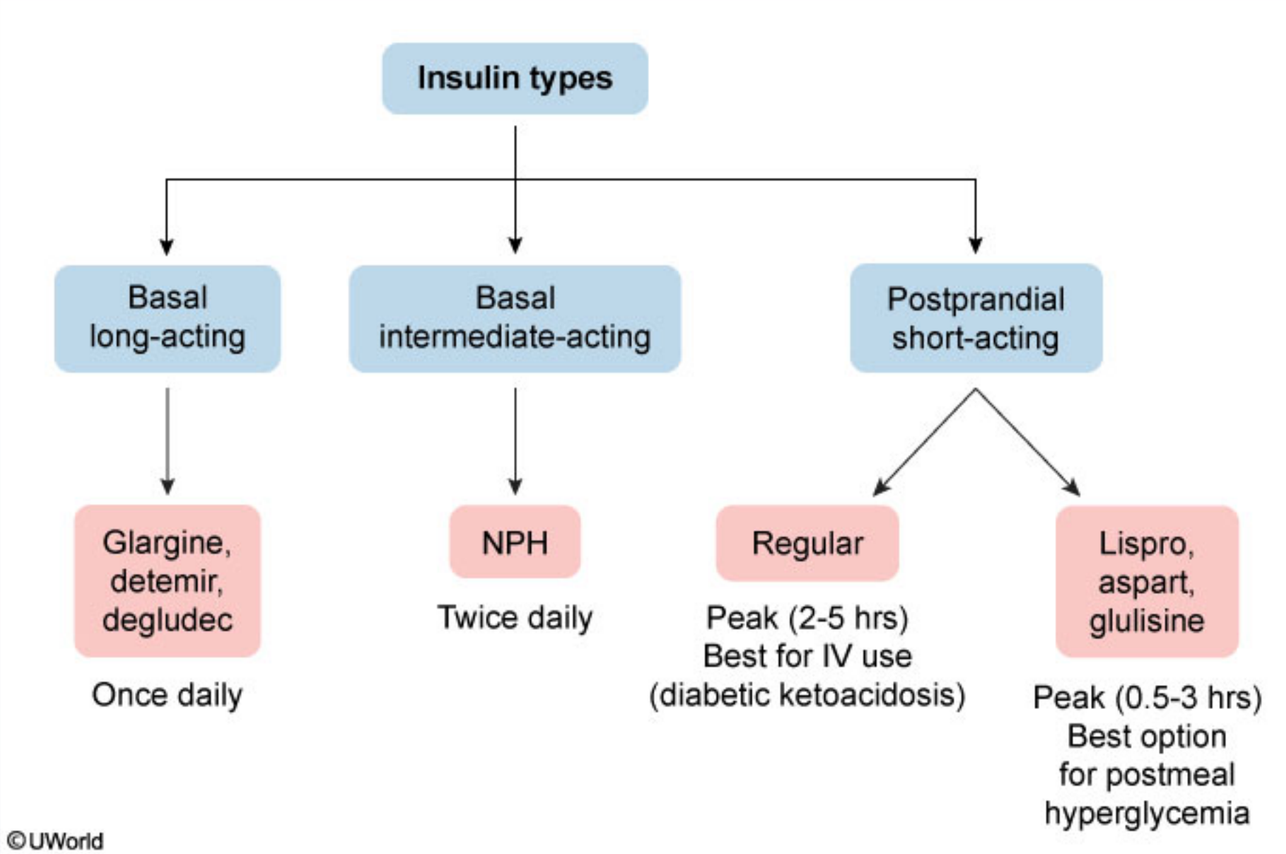
77%
Answered correctly

01 sec
Time Spent

06/09/2020
Last Updated

Explanation

Insulin types



The beta cells of the pancreas produce insulin continuously at a low level. After meals, insulin secretion increases briefly to control the postprandial rise in blood glucose. Commercial insulin analogs are formulated with different pharmacokinetic properties that can be used to replicate physiologic insulin secretion:

- Long-acting insulins have an extended duration of action and little or no peak in activity. They are typically given once daily to mimic basal insulin secretion.
- Rapid-acting insulins are quickly taken up from the injection site and then rapidly cleared. They are given at mealtimes to replicate the

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- Rapid-acting insulins are quickly taken up from the injection site and then rapidly cleared. They are given at mealtimes to replicate the normal postprandial increase in insulin secretion.

This patient has normal fasting glucose levels, suggesting that his long-acting basal insulin therapy is appropriate. However, his postprandial glucose readings are elevated. Adding a **rapid-acting insulin analog** (eg, **aspart**, lispro, glulisine) with meals would **reduce postprandial glucose** and improve overall glycemic control. Because the rapid-acting insulins are cleared quickly, they have minimal residual effect on fasting glucose levels. Regular insulin also can be given at mealtimes but forms dimers and hexamers, which cause a slight delay in uptake from the injection site and prolongation of effect.

(Choices B, C, and D) Insulin degludec has addition of a hexadecanedioic acid residue, which causes polymer formation at the injection site and slowed uptake. Detemir has a fatty acid side chain added to lysine B29 of the insulin molecule, which causes it to bind circulating albumin and slowly dissociate. Glargine has a pH of 4 and forms a microprecipitate at the injection site, resulting in delayed absorption. These analogs all have a long duration of action with minimal peak and are used for basal insulin therapy. As such, they would be poor choices for controlling postprandial glucose.

(Choice E) NPH is a crystalline suspension of insulin with protamine and zinc, which delays absorption from the injection site. NPH is an intermediate-acting insulin that is typically given twice daily; although it has a noticeable peak effect, it is used primarily as basal insulin.

Educational objective:
Long-acting insulin analogs (eg, degludec, detemir, glargine) have an extended duration of action without a noticeable peak in activity and are typically given once daily to mimic basal insulin secretion. Rapid-acting insulins (eg, aspart, lispro, glulisine) are quickly absorbed from the injection site and are given at mealtimes to replicate postprandial insulin secretion.

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References

- Insulin analogs: glimpse on contemporary facts and future prospective.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 35-year-old woman comes to the emergency department due to a "racing heart" and shortness of breath. She has had insomnia and increasing anxiety for the past several weeks. The patient has no prior medical problems and takes no medications. She has no drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/70 mm Hg and pulse is 120/min. Physical examination shows a diffusely enlarged, warm thyroid gland. There is a fine tremor in her outstretched hands. ECG shows sinus tachycardia. Serum TSH is decreased and free thyroxine (T4) is increased. The patient is treated with multiple drugs, including propranolol. In addition to its beta-adrenergic receptor-blocking activity, this drug is likely to decrease which of the following?

- A. Binding of triiodothyronine (T3) to its receptors
- B. New thyroid hormone synthesis
- C. Peripheral conversion of T4 to T3
- D. Release of T4 by the thyroid gland
- E. Serum levels of TSH receptor antibodies

Submit

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- A. Binding of triiodothyronine (T3) to its receptors (11%)
- B. New thyroid hormone synthesis (7%)
- ✓ C. Peripheral conversion of T4 to T3 (69%)
- D. Release of T4 by the thyroid gland (9%)
- E. Serum levels of TSH receptor antibodies (1%)

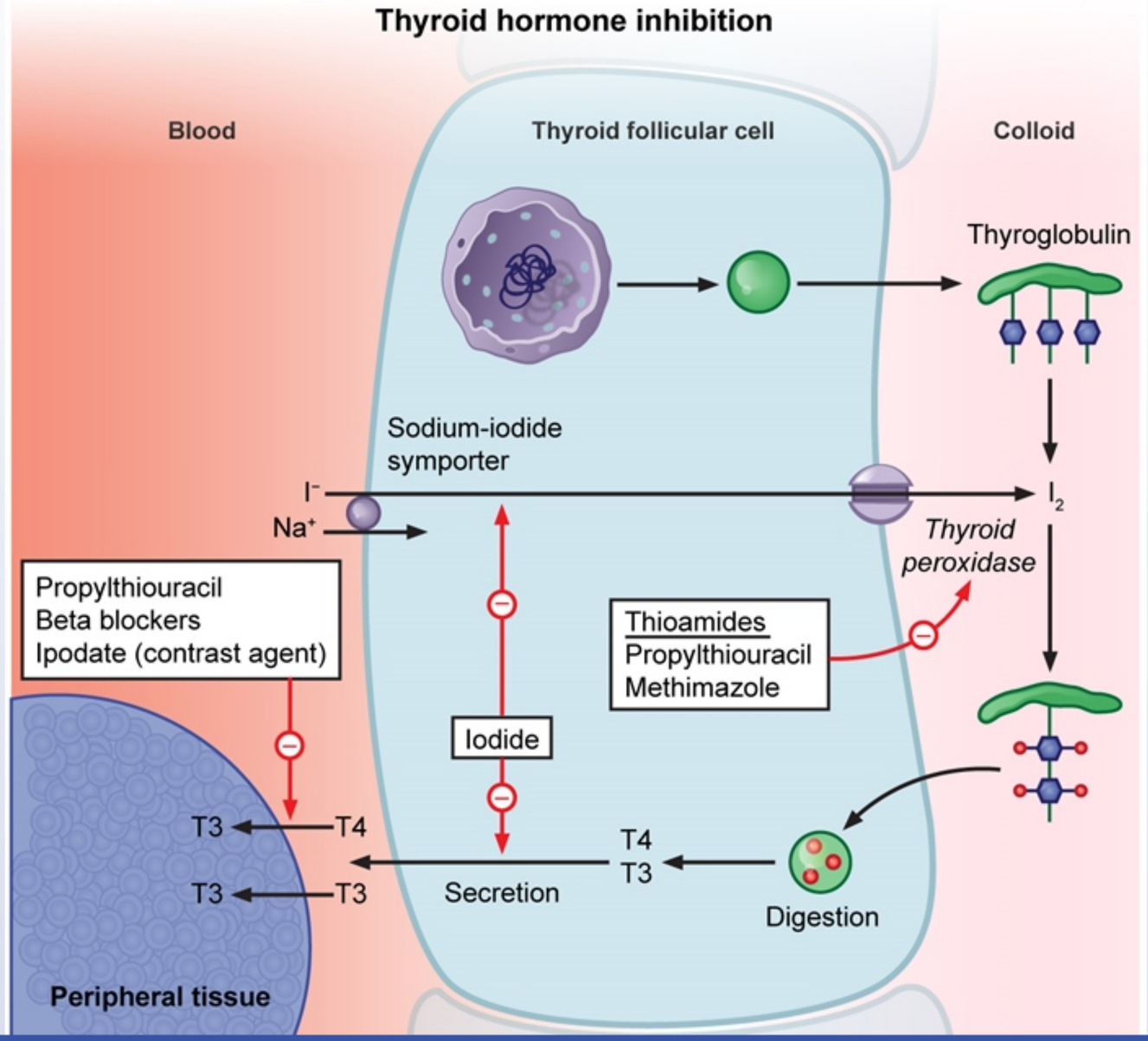
Omitted
Correct answer
C

69%
Answered correctly

02 secs
Time Spent

03/09/2020
Last Updated

Explanation


Thyroid hormone inhibition
Blood
Thyroid follicular cell
Colloid
Thyroglobulin
Sodium-iodide symporter
I⁻
Na⁺
I2
Thyroid peroxidase
Propylthiouracil
Beta blockers
Ipodate (contrast agent)
Thioamides
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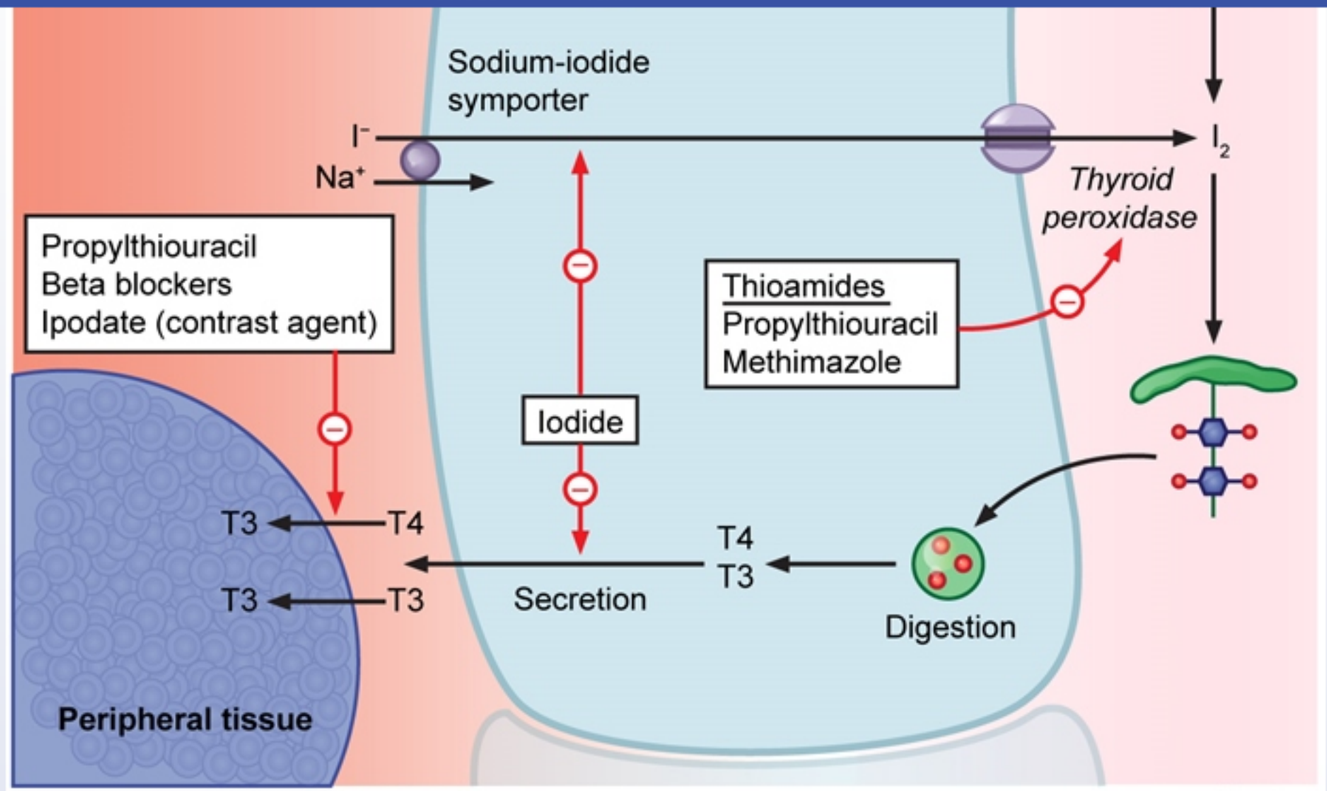
Methimazole
Iodide
T3
T4
T3
T3
T4
T3
Secretion
Digestion
Peripheral tissue



T3 = triiodothyronine; T4 = thyroxine. ©UWorld

This patient has primary **hyperthyroidism** with an elevated thyroxine (T4) and suppressed TSH level. In light of her diffuse goiter, this is likely due to Graves disease. Hyperthyroidism causes upregulation of beta-adrenergic receptor expression, leading to increased catecholamine effect manifesting as hypertension, palpitations/tachycardia, heat intolerance, tremor, and hyperreflexia.

Beta blockers (eg, propranolol) are used to blunt the adrenergic manifestations of hyperthyroidism while awaiting definitive management (eg, surgery, radioiodine). In addition, lipid-soluble beta blockers (including propranolol) reduce conversion of T4 to triiodothyronine (T3), the more active form of thyroid hormone, by inhibiting 5'-monodeiodinase in peripheral tissues. Peripheral conversion of T4 to T3 is also decreased by glucocorticoids and propylthiouracil.

(Choice A) The thyroid hormone receptor functions as a transcriptional modulator of several thyroid hormone–responsive genes. It is an

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(Choice A) The thyroid hormone receptor functions as a transcriptional modulator of several thyroid hormone–responsive genes. It is an intranuclear protein, and binding is not affected by beta blockers.

(Choices B and D) Thionamides (eg, propylthiouracil, methimazole) decrease thyroid hormone synthesis by inhibiting thyroid peroxidase. Iodine inhibits release of T4 and T3 from the thyroid. However, beta blockers do not alter thyroid hormone synthesis or release.

(Choice E) Graves disease is caused by autoantibodies that bind and stimulate the TSH receptor. Glucocorticoids and other immunosuppressive agents can decrease production of these antibodies, but beta blockers do not affect serum levels of TSH receptor antibodies.

Educational objective:
Hyperthyroidism causes upregulation of beta-adrenergic receptor expression, leading to increased catecholamine effect. Beta blockers are used to blunt the adrenergic manifestations of hyperthyroidism. In addition, lipid-soluble beta blockers reduce conversion of T4 to T3 by inhibiting 5'-monodeiodinase in peripheral tissues.

Pharmacology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

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A 64-year-old man comes to the physician complaining of a 6-month history of difficulty urinating with frequent straining and dribbling. His symptoms have increased over time and affect his quality of life significantly. The physician proceeds with drug therapy, which gives the patient moderate symptomatic relief. However, he also notices an increase in hair growth over his scalp. Which of the following is the best description of this drug's mechanism of action?

- A. Decreased Leydig cell stimulation by LH
- B. Decreased Leydig cell androgen synthesis
- C. Decreased peripheral androgen aromatization
- D. Decreased peripheral androgen 5-alpha-reduction
- E. Impaired androgen-receptor interaction
- F. Impaired second messenger action

Submit

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- A. Decreased Leydig cell stimulation by LH (1%)
- B. Decreased Leydig cell androgen synthesis (2%)
- C. Decreased peripheral androgen aromatization (7%)
- ✓ D. Decreased peripheral androgen 5-alpha-reduction (82%)
- E. Impaired androgen-receptor interaction (5%)
- F. Impaired second messenger action (1%)

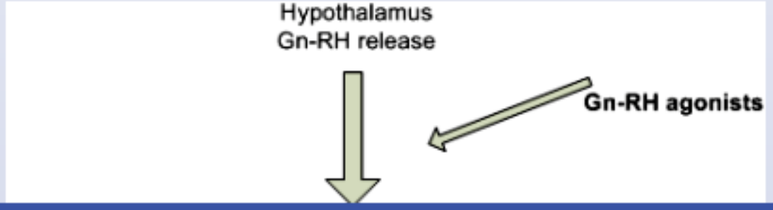
Omitted
Correct answer
D

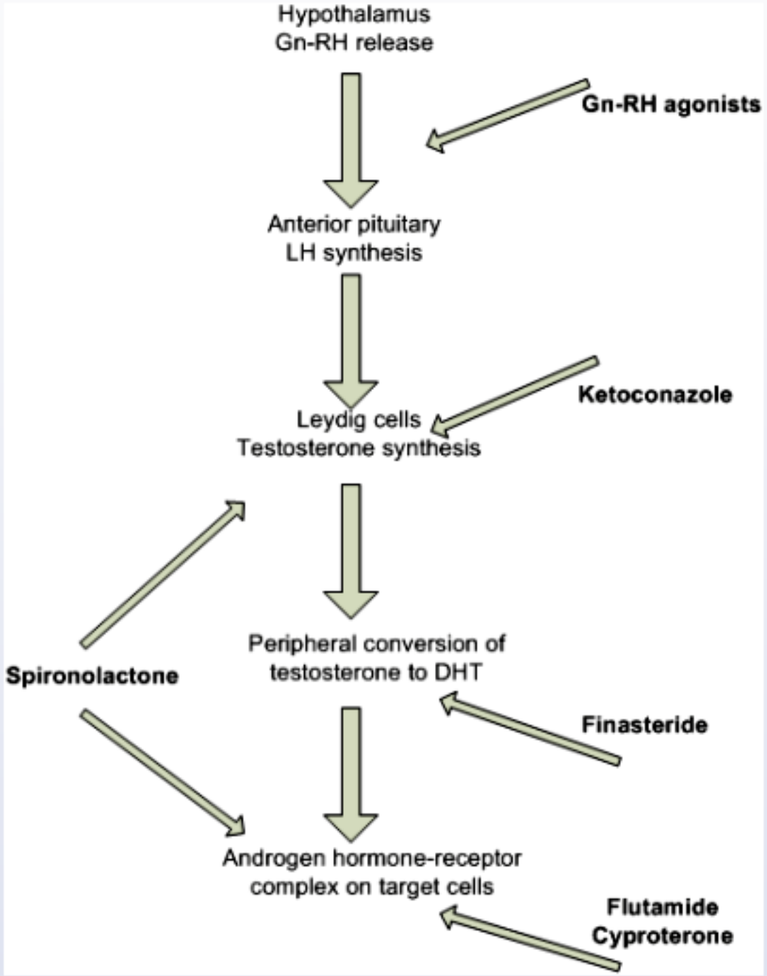
82%
Answered correctly

02 secs
Time Spent

06/23/2020
Last Updated

Explanation





Finasteride is an anti-androgen that inhibits the action of 5-alpha-reductase. This enzyme is responsible for peripheral conversion of testosterone to its active metabolite, dihydrotestosterone (DHT). DHT has a much higher affinity for the testosterone receptor and mediates the majority of testosterone effects, including development of male external genitalia and prostate enlargement. Finasteride counteracts these effects of DHT and is used for treatment of benign prostatic hyperplasia (BPH).

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Patients with androgenetic alopecia have higher levels of 5-alpha-reductase and a higher quantity of androgen receptors. Thus, reducing the 5-alpha-reductase level with finasteride is also useful for treating androgenetic alopecia.

(Choice A) Decreased Leydig cell stimulation by LH occurs during treatment with GnRH agonists (leuprolide, goserelin, nafarelin, and histrelin). Finasteride does not affect LH synthesis by the anterior pituitary.

(Choice B) Ketoconazole is a weak anti-androgen that decreases synthesis of testosterone in the Leydig cells of the testes. It also inhibits steroid hormone production by the adrenals.

(Choice C) Decreased peripheral androgen aromatization occurs with anastrozole, an aromatase inhibitor that selectively blocks estrogen production. Anastrozole is an effective treatment for postmenopausal women with breast cancer. In these women, the greatest source of estrogen is the conversion of *androstenedione*, produced in the adrenal glands, to *estrone* through aromatization in liver, muscle, and fat.

(Choice E) The interaction of testosterone and DHT with their receptors is inhibited by flutamide, cyproterone acetate, and spironolactone. Flutamide is used to treat metastatic prostate cancer, but not BPH due to its significant antiandrogenic side effects.

(Choice F) Finasteride does not affect second messenger action.

Educational objective:
Finasteride is a 5-alpha-reductase inhibitor that suppresses peripheral conversion of testosterone to dihydrotestosterone. It is used for treatment of benign prostatic hyperplasia and androgenetic alopecia.

Pharmacology	Endocrine, Diabetes & Metabolism	Benign prostatic hyperplasia
Subject	System	Topic

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A 54-year-old woman comes to the office for evaluation of elevated blood glucose. The patient was recently seen at an urgent care center, where she was found to have a nonfasting blood glucose level of 190 mg/dL. Medical history is insignificant, although she has not seen a physician for several years. She does not use tobacco or alcohol. BMI is 31.5 kg/m^2. Physical examination shows no abnormalities. Hemoglobin A1c is 8.5% and fasting plasma glucose level is 146 mg/dL. Recommendations for dietary modification and exercise are provided, and pharmacotherapy with metformin is planned. Which of the following laboratory tests should be obtained prior to starting this medication?

A. Blood cell counts and mean corpuscular volume

B. Oral glucose tolerance test

C. Plasma lactate level

D. Serum creatinine level

E. Serum potassium level

F. Serum TSH level

Submit

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- A. Blood cell counts and mean corpuscular volume (2%)
- B. Oral glucose tolerance test (1%)
- C. Plasma lactate level (27%)
- ✓ D. Serum creatinine level (64%)
- E. Serum potassium level (3%)
- F. Serum TSH level (1%)

Omitted
Correct answer
D

64%
Answered correctly

02 secs
Time Spent

03/21/2020
Last Updated

Explanation

Metformin	
Mechanism of action	• Inhibits mitochondrial glycerophosphate dehydrogenase & complex I • Upregulates AMP-activated protein kinase

Metformin	
Mechanism of action	• Inhibits mitochondrial glycerophosphate dehydrogenase & complex I • Upregulates AMP-activated protein kinase
Metabolic effects	• ↓ Hepatic glucose production • ↓ Intestinal glucose absorption • ↑ Peripheral glucose uptake/utilization • ↓ Lipogenesis
Pharmacokinetics	• Renal clearance • No significant metabolites
Adverse effects	• Diarrhea • Lactic acidosis • Vitamin B_{12} deficiency
Precautions/ contraindications	• Renal insufficiency (check serum creatinine) • Hepatic insufficiency • Congestive heart failure

Metformin is the most commonly prescribed medication for type 2 diabetes mellitus. It **reduces hepatic gluconeogenesis** through multiple mechanisms, including inhibition of glycerophosphate dehydrogenase and complex I (the first enzymes in the electron transport chain) and upregulation of AMP-activated protein kinase. These mechanisms reduce the availability of substrates for gluconeogenesis (eg, dihydroxyacetone phosphate, pyruvate, fatty acids) and **increase peripheral glucose uptake** and utilization. Metformin does not increase endogenous insulin secretion and is therefore less likely to cause hypoglycemia than sulfonylureas or insulin.

The inhibition of gluconeogenic enzymes by metformin results in buildup of substrate molecules that are released into the plasma; decreased formation of pyruvate results in excess buildup of its precursor, lactate, which increases the risk of **lactic acidosis**. Although rare, the risk is increased in those with significant **renal dysfunction** or other disorders causing decreased lactate clearance (eg, hepatic impairment, congestive heart failure). For this reason, the glomerular filtration rate should be estimated using **serum creatinine measurement** prior to initiation of

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(Choice A) Metformin can cause vitamin B_{12} deficiency, likely due to decreased intestinal absorption. However, this is a chronic effect seen after long-term use, and preprescription testing is not needed.

(Choice B) The oral glucose tolerance test can be used for initial diagnosis of diabetes or primarily gestational diabetes. This patient's diagnosis has been confirmed with the elevated fasting glucose and hemoglobin A1c; additional diagnostic testing is not necessary.

(Choice C) Plasma lactate levels are used to confirm acute lactic acidosis; measurement of a baseline level is not necessary.

(Choice E) Monitoring serum potassium is not necessary with metformin use. Serum potassium is routinely monitored with diuretics (especially loop diuretics), spironolactone, ACE inhibitors, and angiotensin II receptor blockers.

(Choice F) Thyroid function tests are not required for any antidiabetic medications, including metformin. They are routinely performed in patients taking lithium and amiodarone.

Educational objective:
Metformin inhibits hepatic gluconeogenesis and increases peripheral glucose utilization. Lactic acidosis is a rare complication of metformin therapy, but its risk is increased in patients with underlying renal insufficiency.

References

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Metformin inhibits hepatic gluconeogenesis and increases peripheral glucose utilization. Lactic acidosis is a rare complication of metformin therapy, but its risk is increased in patients with underlying renal insufficiency.

References

- Metformin-associated lactic acidosis: predisposing factors and outcome.
- Metformin in patients with type 2 diabetes and kidney disease: a systematic review.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 57-year-old woman comes to the office due to left breast pain associated with fatigue, nausea, and unexplained weight loss. She is referred for mammography, which reveals a 3-cm dominant mass in the left breast. Biopsy confirms the mass to be adenocarcinoma, and subsequent studies find that the tumor is estrogen receptor-positive and human epidermal growth factor receptor 2- (HER2) negative. The patient experienced menopause at age 52, and her past medical history is otherwise unremarkable. Anastrozole treatment is initiated and leads to a substantial decrease in the size of the primary tumor. Which of the following is the best explanation for the therapeutic effect of this agent?

A. Decreased androgen aromatization

B. Decreased androgen synthesis

C. Decreased follicular cell stimulation

D. Impaired ligand-receptor interaction

E. Impaired second-messenger action

Submit

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- ✓ A. Decreased androgen aromatization (70%)
- B. Decreased androgen synthesis (9%)
- C. Decreased follicular cell stimulation (3%)
- D. Impaired ligand-receptor interaction (14%)
- E. Impaired second-messenger action (2%)

Omitted
Correct answer
A

70%
Answered correctly

01 sec
Time Spent

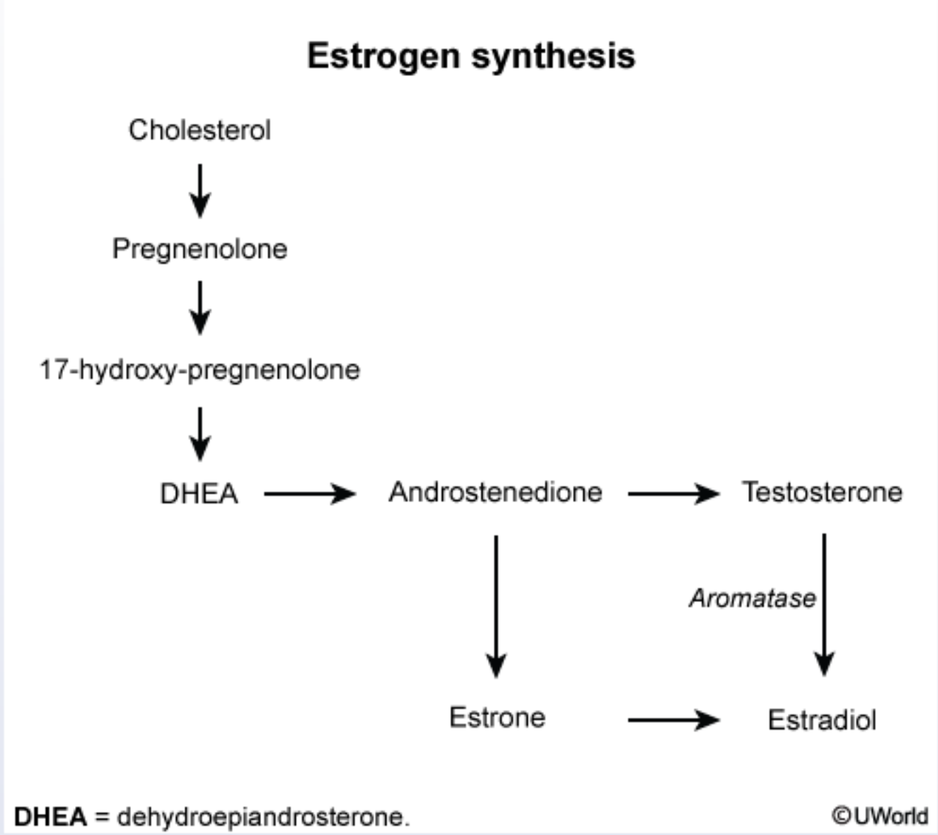
02/20/2020
Last Updated

Explanation

Estrogen synthesis

Cholesterol

↓



Estrogens are synthesized primarily by the aromatization of androgens. **Aromatase** belongs to the P450 superfamily and is highly expressed in **ovarian tissue** (in which expression is **gonadotropin dependent**). Aromatase is also expressed in the adrenal cortex, subcutaneous fat, and breast. In the postmenopausal state, follicular atresia leads to reduced numbers of granulosa cells and decreased ovarian estrogen synthesis. However, the ovaries and adrenal glands continue to produce androgens in significant quantities, and **extraovarian aromatase** maintains a low level of estrogen in the peripheral circulation.

Estrogen is the main hormone driving the growth and development of estrogen receptor (ER)-positive malignant breast tumors. **Aromatase inhibitors** (eg, anastrozole, letrozole, exemestane) reduce the synthesis of estrogen from androgens, suppressing estrogen levels in postmenopausal women and **slowing progression of ER-positive tumors**. They are less effective as monotherapy in premenopausal women

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(Choice B) Although inhibition of androgen synthesis could theoretically decrease estrogen synthesis, most androgen synthesis inhibitors (eg, ketoconazole) are nonspecific and suppress other pathways of steroidogenesis (eg, cortisol, mineralocorticoid).

(Choice C) Pulsatile stimulation of the pituitary by gonadotropin-releasing hormone (GnRH) increases secretion of LH and FSH. However, continuous GnRH stimulation by long-acting GnRH analogs (eg, goserelin) suppresses LH and FSH release, decreasing production of estrogens in the ovarian follicle. These agents are useful for ovarian suppression in premenopausal women with ER-positive breast cancer.

(Choice D) Tamoxifen acts as either an antagonist or a partial agonist of the estrogen receptor, depending on the tissue. In breast tissue, tamoxifen antagonizes the estrogen receptor and can be used as adjuvant therapy for ER-positive breast cancer.

(Choice E) Many breast cancers overexpress epidermal growth factor receptor 2 (HER2). Trastuzumab is a monoclonal antibody against HER2 that is used in patients with HER2-positive tumors. It inhibits MAPK and PI3K/Akt signaling pathways, increases degradation of HER2, and facilitates antibody-mediated destruction of tumor cells.

Educational objective:
Estrogen is the main hormone responsible for the growth and development of estrogen receptor (ER)-positive breast tumors. Aromatase inhibitors (eg, anastrozole, letrozole, exemestane) decrease the synthesis of estrogen from androgens, suppressing estrogen levels and slowing progression of ER-positive tumors.

References

Estrogen is the main hormone driving the growth and development of estrogen receptor (ER)-positive malignant breast tumors. **Aromatase inhibitors** (eg, anastrozole, letrozole, exemestane) reduce the synthesis of estrogen from androgens, suppressing estrogen levels in postmenopausal women and **slowing progression of ER-positive tumors**. They are less effective as monotherapy in premenopausal women, as ovarian aromatase is upregulated substantially in response to gonadotropins.

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References

- Aromatase inhibitors in breast cancer.

Pharmacology	Endocrine, Diabetes & Metabolism	Aromatase inhibitors
Subject	System	Topic

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A 22-year-old woman comes to the emergency department due to fever and a sore throat. Her medical history is significant for Graves disease, for which she recently began taking an antithyroid medication. The patient has no other medical conditions and does not use tobacco, alcohol, or illicit drugs. She works as a teacher at an elementary school. Temperature is 38.9 C (102 F), blood pressure is 110/70 mm Hg, and pulse is 90/min. Physical examination shows an erythematous pharynx and a normal-sized thyroid. There is no tremor of the outstretched hands. Which of the following is the most likely cause of this patient's current condition?

A. Acute adrenal insufficiency

B. Drug-induced granulocyte destruction

C. Excessive thyroid suppression

D. Thyroid hormone–induced severe hypermetabolism

E. Viral destruction of neutrophils

Submit

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- A. Acute adrenal insufficiency (1%)
- ✓ B. Drug-induced granulocyte destruction (68%)
- C. Excessive thyroid suppression (5%)
- D. Thyroid hormone–induced severe hypermetabolism (3%)
- E. Viral destruction of neutrophils (20%)

Omitted
Correct answer
B

68%
Answered correctly

02 secs
Time Spent

04/30/2020
Last Updated

Explanation

Complications of Graves disease treatment	
Treatment	**Adverse effects**
Antithyroid drugs	• **Agranulocytosis** • Methimazole: 1st-trimester teratogen

Explanation

Complications of Graves disease treatment	
Treatment	**Adverse effects**
Antithyroid drugs (thionamides)	• **Agranulocytosis** • Methimazole: 1st-trimester teratogen • Propylthiouracil: **Hepatic failure**
Radioiodine ablation	• Permanent hypothyroidism • Worsening of ophthalmopathy • Possible radiation side effects
Surgery	• Permanent hypothyroidism • Risk of recurrent laryngeal nerve damage • Risk of hypoparathyroidism

Antithyroid drugs (eg, propylthiouracil [PTU], methimazole) inhibit thyroid peroxidase and are used to decrease thyroid hormone production in patients with hyperthyroidism (eg, Graves disease). However, antithyroid drugs are associated with an increased risk for **agranulocytosis**, typically in the first few months of therapy. This is an idiosyncratic and potentially life-threatening side effect of therapy and is likely due to both immune-mediated effects (via generation of antineutrophil cytoplasmic antibodies) and direct bone marrow toxicity (via generation of reactive oxygen species).

Patients with drug-induced agranulocytosis (absolute neutrophil count <500/mm^3) are at risk for **severe infection**; oropharyngeal infection (eg, fever, **sore throat**, **oral ulcerations**) is the most common initial manifestation, and sepsis can develop quickly thereafter. **Complete blood count with differential** will show **neutropenia** without anemia or thrombocytopenia; bone marrow biopsy will reveal a reduction in granulocyte precursors. Agranulocytosis is reversible on **discontinuation of the drug**.

(Choice A) Patients with autoimmune thyroid disease are at risk for other autoimmune endocrinopathies, including adrenal insufficiency. However, acute adrenal crisis typically presents with refractory hypotension, vomiting, abdominal pain, and weakness.

	• Risk of hypoparathyroidism

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(Choices C and D) Excessive suppression of thyroid function by antithyroid drugs leads to a hypothyroid state characterized by fatigue, weight gain, cold intolerance, and hair and skin changes. Undertreatment would result in a residual hyperthyroid state, with anxiety, tachycardia, tremor, and heat intolerance. Neither hyper- nor hypothyroidism typically present with a febrile pharyngeal infection.

(Choice E) A number of viruses can cause neutropenia, including HIV, viral hepatitis (A, B, C), and the herpesvirus group (varicella zoster virus, Epstein-Barr virus, cytomegalovirus, human herpesvirus-6). However, the recent initiation of an antithyroid drug makes drug-induced agranulocytosis more likely.

Educational objective:
Agranulocytosis is a serious complication of antithyroid drugs (eg, methimazole, propylthiouracil) that results from drug-induced granulocyte destruction and consequent neutropenia. Initial manifestations often include fever, sore throat, and oral ulcerations. If drug-induced agranulocytosis is suspected, the drug should be discontinued immediately and a complete blood count with differential should be obtained to help confirm the diagnosis.

References

- Risk of hypoparathyroidism

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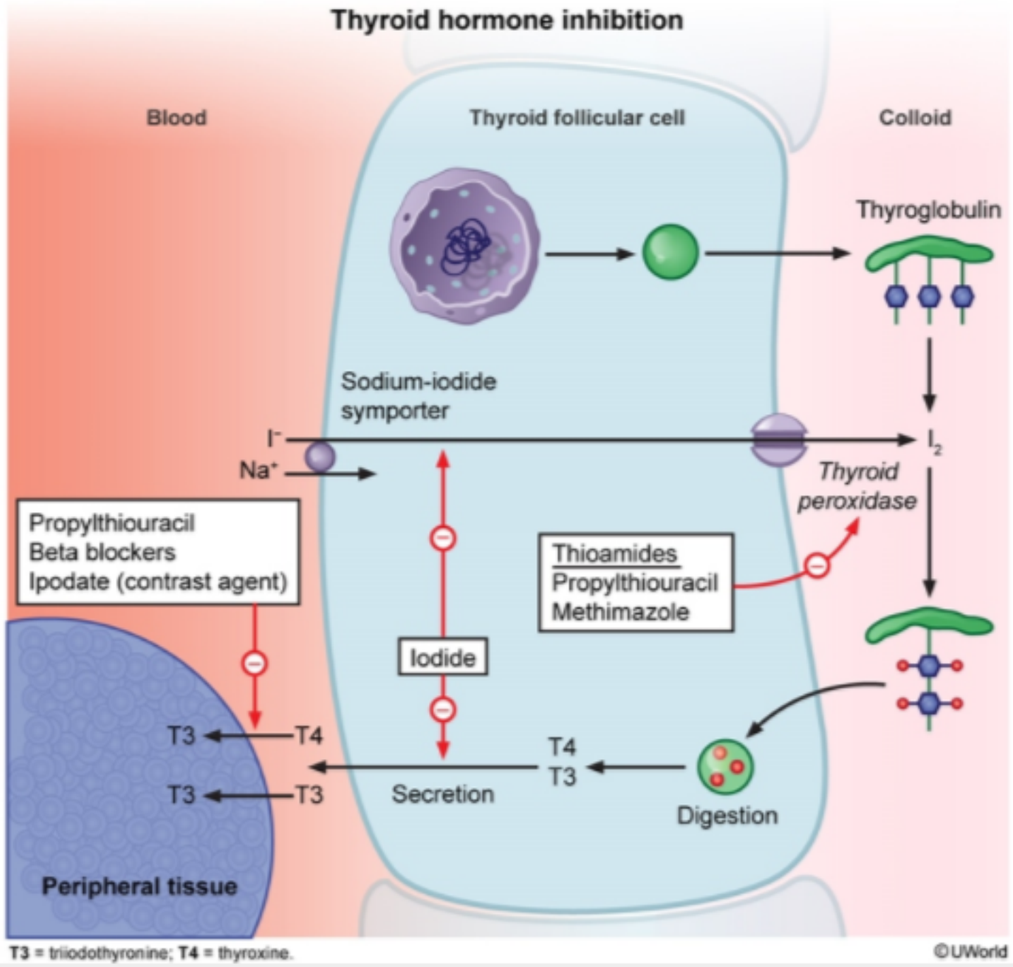

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References

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References

- Antithyroid drug-induced agranulocytosis: state of the art on diagnosis and management.

Pharmacology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

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A 22-year-old woman comes to the office due to palpitations, weight loss, and insomnia. She has lost 7 kg (15.4 lb) in the past 3 months. The patient has no other medical problems and takes no medication. She does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/80 mm Hg and pulse is 104/min and regular. The thyroid gland is diffusely enlarged and nontender on palpation. Laboratory studies show markedly decreased serum TSH and elevated thyroxine levels. Methimazole monotherapy is initiated. Two months later, her symptoms had resolved. The treatment most likely improved this patient's condition by directly inhibiting which of the following processes?

- A. Colloid production
- B. Coupling of iodotyrosines
- C. Iodide uptake by the thyroid gland
- D. Peripheral thyroxine to triiodothyronine conversion
- E. Triiodothyronine/thyroxine effect on target tissues

Submit

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- A. Colloid production (1%)
- ✓ B. Coupling of iodotyrosines (74%)
- C. Iodide uptake by the thyroid gland (7%)
- D. Peripheral thyroxine to triiodothyronine conversion (14%)
- E. Triiodothyronine/thyroxine effect on target tissues (1%)

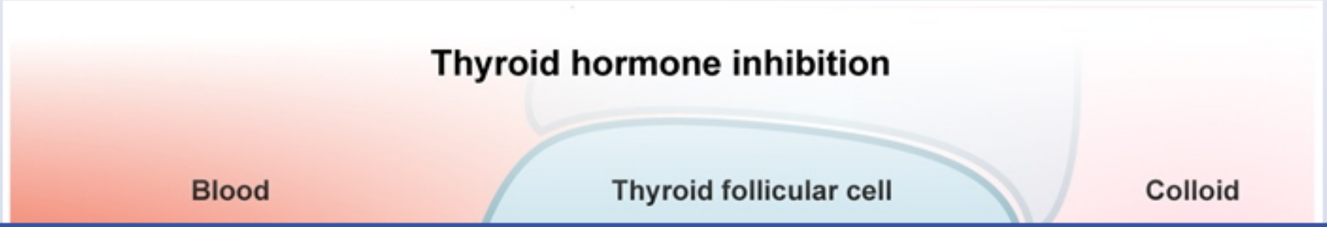
Omitted
Correct answer
B

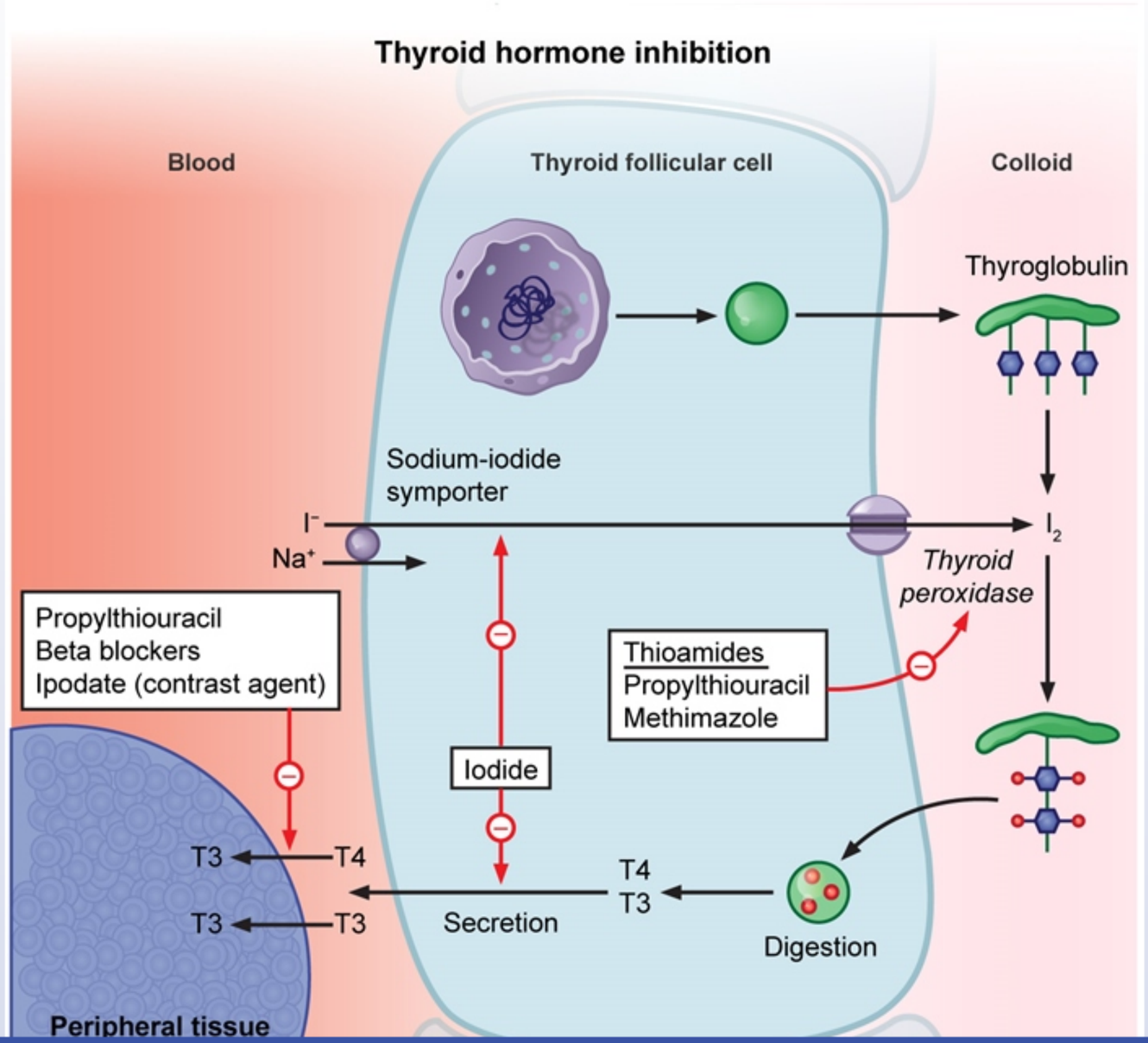
74%
Answered correctly

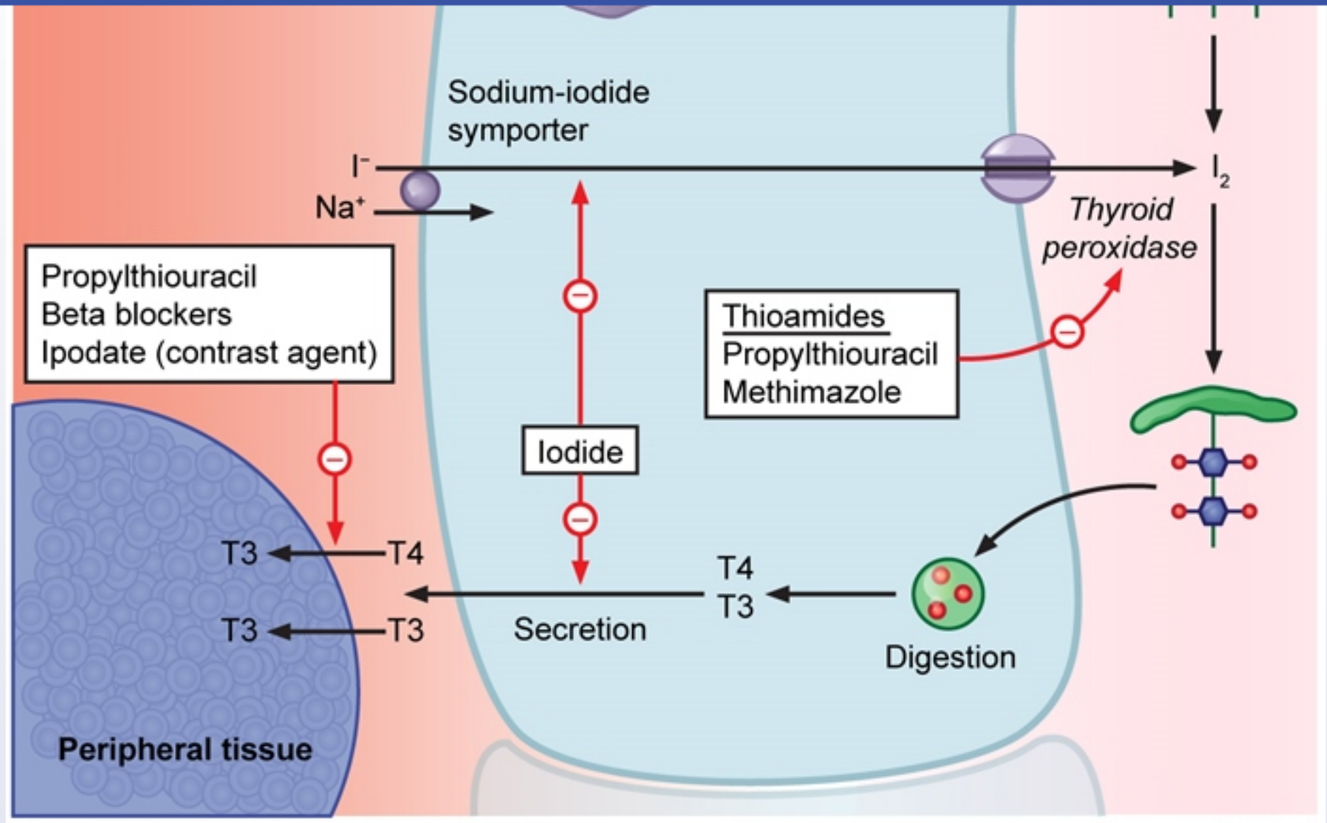
02 secs
Time Spent

03/15/2020
Last Updated

Explanation




Thyroid hormone inhibition
Blood
Thyroid follicular cell
Colloid
Thyroglobulin
Sodium-iodide symporter
I⁻
Na⁺
I2
Thyroid peroxidase
Propylthiouracil
Beta blockers
Ipodate (contrast agent)
Thioamides
Propylthiouracil
Methimazole
Iodide
T3
T4
T3
T3
T4
T3
Secretion
Digestion
Peripheral tissue



T3 = triiodothyronine; **T4** = thyroxine. ©UWorld

Thyroid follicular cells take up inorganic iodide (iodide trapping) against a concentration gradient using a sodium-iodide symporter. Iodide is then released into the thyroid follicular lumen, where it is oxidized to iodine radical by thyroid peroxidase. Iodine then binds to tyrosine residues (organification) in thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). Coupling of MIT and DIT produces triiodothyronine (T3; MIT coupled with DIT) and thyroxine (T4; two DITs coupled). The thyroid follicular cells then engulf thyroglobulin, which contains the iodinated tyrosine compounds, via pinocytosis. In the thyroid cytoplasm, T3 and T4 (collectively, thyroid hormones) are removed from the rest of the thyroglobulin and secreted from the basolateral border.

This patient with elevated T4 and suppressed TSH has primary **hyperthyroidism**. Methimazole and propylthiouracil are **thioamide drugs** used for treating hyperthyroidism. They **inhibit thyroid peroxidase**, the enzyme responsible for both **iodine organification** and **coupling of**

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This patient with elevated T4 and suppressed TSH has primary **hyperthyroidism**. Methimazole and propylthiouracil are **thioamide drugs** used for treating hyperthyroidism. They **inhibit thyroid peroxidase**, the enzyme responsible for both **iodine organification** and **coupling of iodotyrosines**. Propylthiouracil also decreases the peripheral conversion of T4 to the active hormone T3, although methimazole does not have this effect **(Choice D)**.

(Choice A) Colloid is a gelatinous material in the follicular lumen that consists mainly of thyroglobulin. The production of colloid is regulated primarily by TSH; it is not dependent on thyroid peroxidase and is not inhibited by thioamides.

(Choice C) Iodide uptake is upregulated by TSH. Perchlorate and pertechnetate are competitive inhibitors of the sodium-iodide symporter.

(Choice E) Hyperthyroidism is characterized by increased sensitivity to catecholamines due to the thyroid hormone–mediated upregulation of beta-adrenergic receptors. Beta blockers help decrease the target organ effects of thyroid hormones, and certain ones (eg, propranolol) also decrease the peripheral conversion of T4 to T3.

Educational objective:
Thioamides (eg, methimazole, propylthiouracil) decrease the formation of thyroid hormones via inhibition of thyroid peroxidase, the enzyme responsible for both iodine organification and coupling of iodotyrosines. Propylthiouracil also decreases the peripheral conversion of T4 to T3.

Pharmacology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

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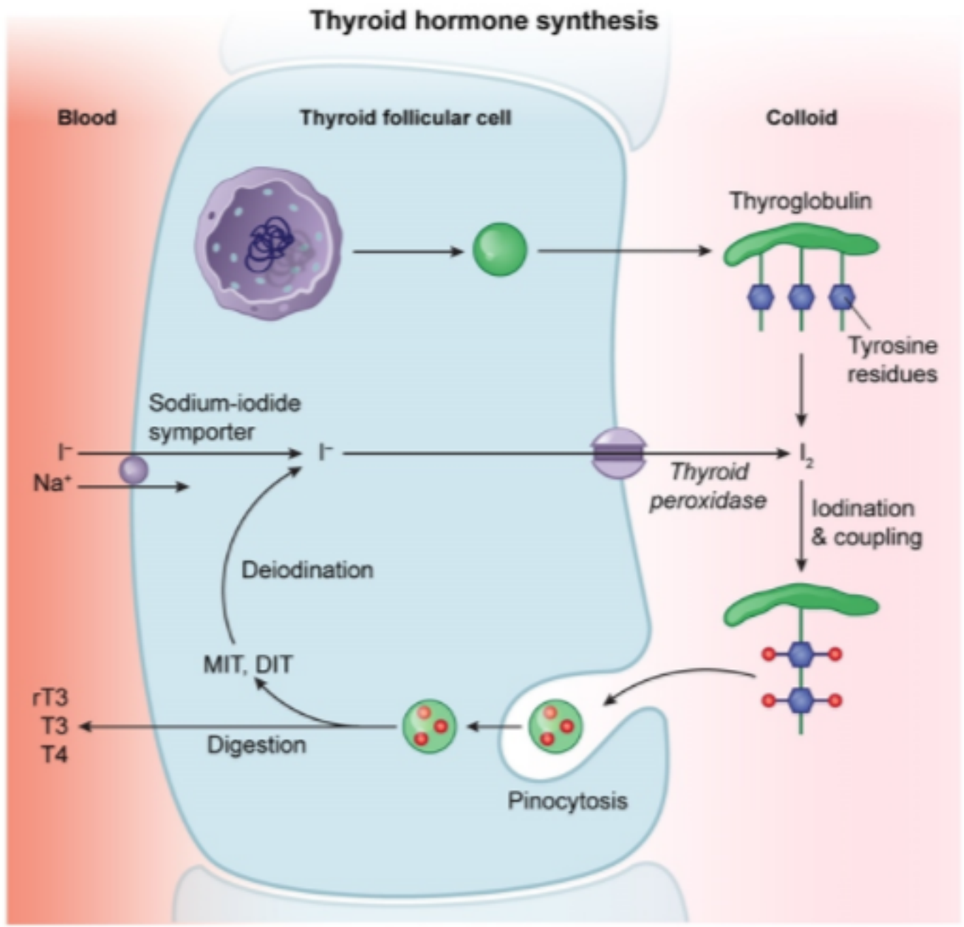
T3 = triiodothyronine; T4 = thyroxine.

©UWorld

Exhibit Display



DIT = diiodotyrosine; rT3 = reverse triiodothyronine; T3 = triiodothyronine; T4 = thyroxine; MIT = monoiodotyrosine.

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A 55-year-old man comes to the emergency department due to progressive weakness and lethargy. The patient says that over the past 3 months he has been excessively thirsty and waking up several times at night to urinate. He has also lost 5 kg (11 lb) during this time despite no change in appetite. The patient has not seen a doctor in several years. Family history is significant for type 2 diabetes mellitus in his mother and father. Blood pressure is 108/60 mm Hg, and pulse is 98/min. BMI is 38 kg/m^2. Physical examination shows dry mucous membranes and poor skin turgor. Laboratory testing reveals a blood glucose concentration of 600 mg/dL. Serum beta-hydroxybutyrate is normal, and hemoglobin A1c is 14%. The patient is admitted, and intravenous fluids and insulin infusion are begun. The next day, his symptoms significantly improve, and the blood glucose levels normalize. In preparation for discharge, his insulin infusion is changed to a subcutaneous regimen that closely mimics the physiologic pattern of insulin release. This patient's insulin therapy was most likely transitioned to which of the following regimens?

A. Combination NPH insulin plus regular insulin twice daily

B. Insulin aspart before each meal

C. Insulin detemir twice daily

D. Insulin glargine once daily

E. Insulin glargine once daily plus insulin lispro before each meal

Submit

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- A. Combination NPH insulin plus regular insulin twice daily (10%)
- B. Insulin aspart before each meal (15%)
- C. Insulin detemir twice daily (0%)
- D. Insulin glargine once daily (1%)
- ✓ E. Insulin glargine once daily plus insulin lispro before each meal (71%)

Omitted
Correct answer
E

71%
Answered correctly

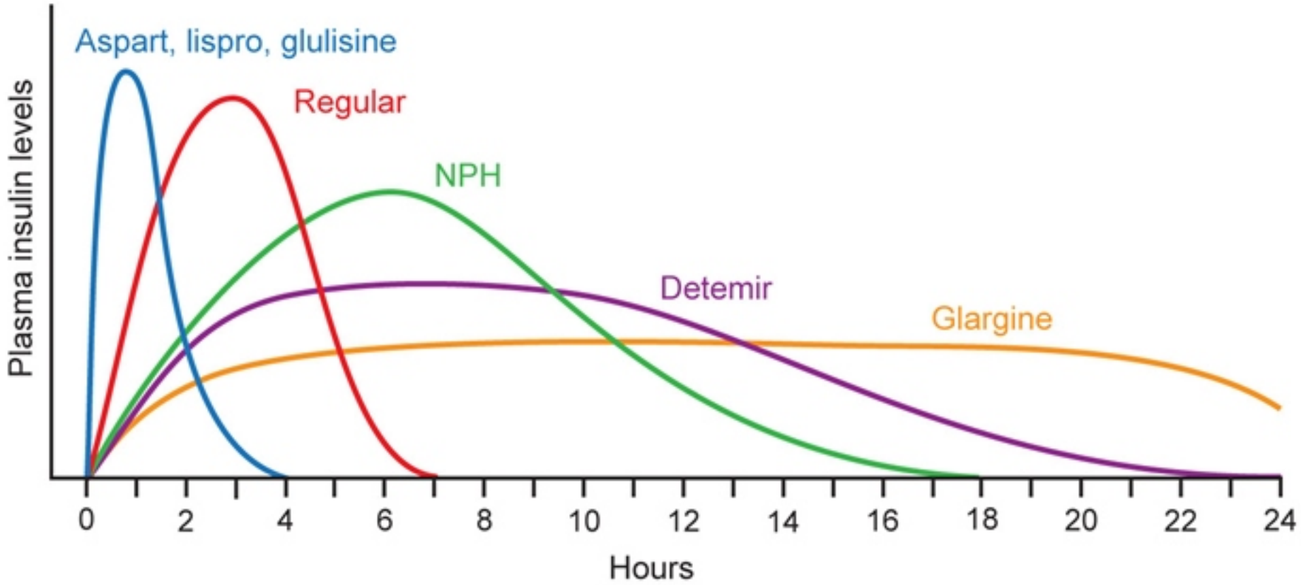
13 secs
Time Spent

05/25/2020
Last Updated

Explanation

Pharmacokinetic profiles of common insulin preparations

Pharmacokinetic profiles of common insulin preparations



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This patient has polyuria, polydipsia, weight loss, and risk factors for **type 2 diabetes mellitus** that include obesity and a positive family history; the striking elevation in hemoglobin A1c confirms the diagnosis. He now has lethargy, dehydration (eg, dry mucous membranes), and severe hyperglycemia that is consistent with a **hyperosmolar hyperglycemic state**, a potential complication of untreated diabetes. He was appropriately managed with intravenous fluids and insulin and now needs to be transitioned to chronic insulin therapy.

Insulin is normally secreted continuously by pancreatic beta cells 24 hours a day (basal insulin secretion). Then, following meals, insulin secretion increases transiently to control the postprandial surge in blood glucose as dietary sugar and digested carbohydrates are absorbed in the intestine.

Physiologic insulin secretion can be approximated by a combination of long-acting and rapid-acting insulin analogs (ie, basal-bolus regimen). **Long-acting preparations** (eg, glargine) are released from the injection site continuously throughout the day and **replicate basal insulin** secretion. Concurrently, boluses of a **rapid-acting insulin** (eg, lispro) that is quickly absorbed are given with each meal to control **postprandial glucose elevations**. Alternately, an insulin pump can provide a steady supply of insulin throughout the day as well as mealtime dose increases.

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(Choice A) A regimen using NPH insulin and regular insulin twice daily does not closely replicate physiologic insulin secretion. NPH is an intermediate-acting insulin that has a significant (and delayed) peak effect, increasing the risk of hypoglycemia between doses. In addition, regular insulin can polymerize at the injection site, causing a short delay in absorption leading to higher postprandial glucose levels.

(Choice B) Insulin aspart alone can replicate postprandial insulin secretion but does not provide basal insulin effect.

(Choices C and D) Insulin glargine alone provides a basal insulin effect, while insulin detemir, given once or twice daily, has a shorter duration of effect than glargine but can be used as basal insulin in some patients; however, neither provides appropriate mealtime coverage to control postprandial glucose.

Educational objective:
Physiologic insulin secretion can be approximated by a combination of long-acting and rapid-acting insulin analogs. Long-acting preparations (eg, glargine) are released from the injection site slowly throughout the day and replicate basal insulin secretion. Boluses of a rapid-acting insulin (eg, lispro) with quick absorption are given with meals to control postprandial glucose elevations.

References

- A review of basal-bolus therapy using insulin glargine and insulin lispro in the management of diabetes mellitus.

A 53-year-old man comes to the office due to uncontrolled type 2 diabetes mellitus. Three years ago, the patient was diagnosed with diabetes and started on metformin and lifestyle modification. In the past year, his hemoglobin A1c level has been steadily rising. Blood pressure is 145/90 mm Hg. BMI is 37 kg/m^2. Laboratory results are normal except for a fasting plasma glucose of 155 mg/dL and a hemoglobin A1c level of 8%. Additional treatment with canagliflozin is initiated. Over the next several days, which of the following changes are most likely to occur in this patient due to the new medication?

	Urinary glucose excretion	Total body sodium content	Extracellular fluid volume
A.	Decreased	Decreased	Unchanged
B.	Decreased	Increased	Decreased
C.	Increased	Decreased	Decreased
D.	Increased	Unchanged	Increased
E.	Increased	Increased	Decreased

Submit

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	Urinary glucose excretion	Total body sodium content	Extracellular fluid volume
A. (1%)	Decreased	Decreased	Unchanged
B. (1%)	Decreased	Increased	Decreased
✓ C. (74%)	Increased	Decreased	Decreased
D. (8%)	Increased	Unchanged	Increased
E. (14%)	Increased	Increased	Decreased

Omitted
Correct answer
C

74%
Answered correctly

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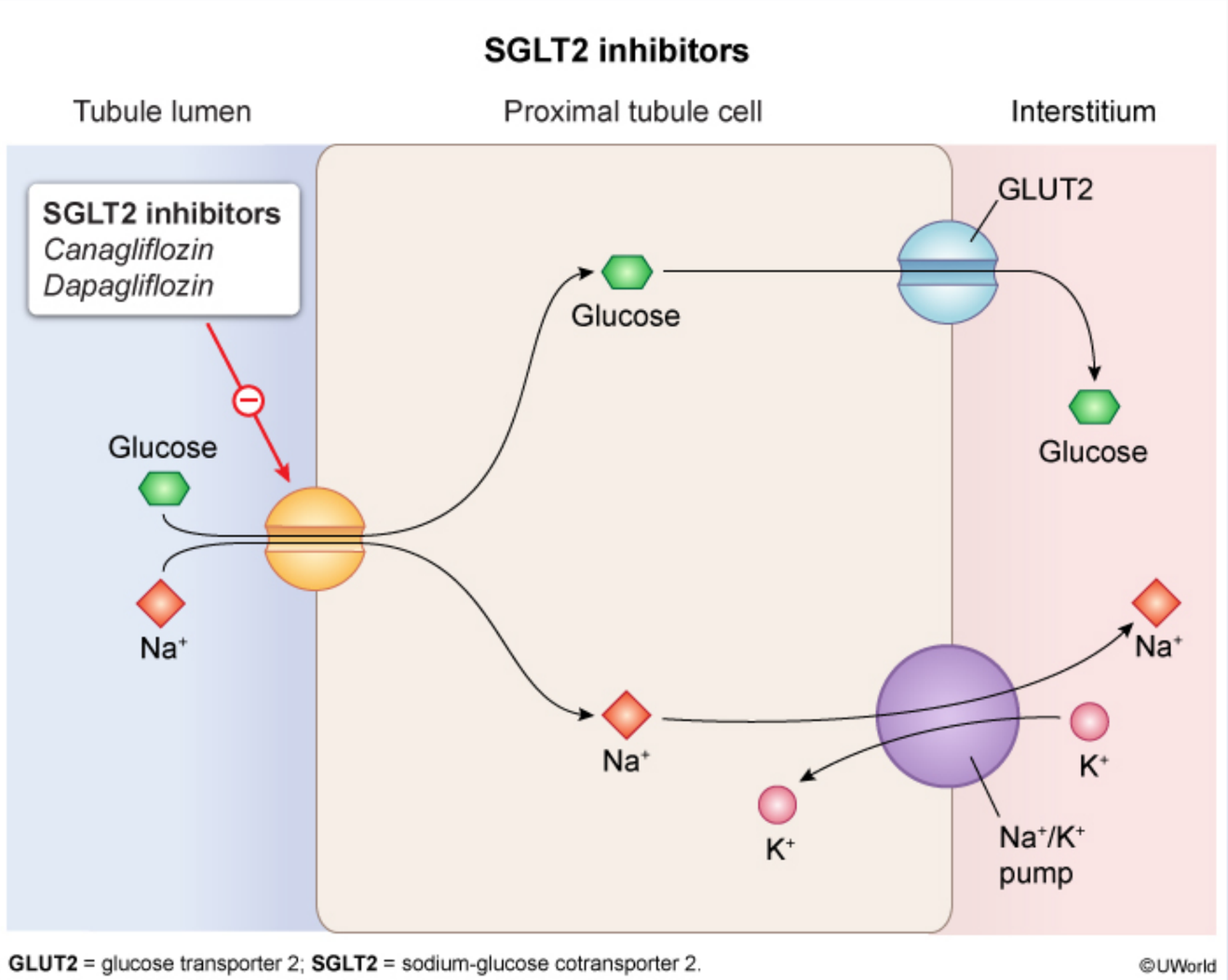
Time Spent

05/13/2020
Last Updated

Explanation

Explanation



GLUT2 = glucose transporter 2; **SGLT2** = sodium-glucose cotransporter 2.

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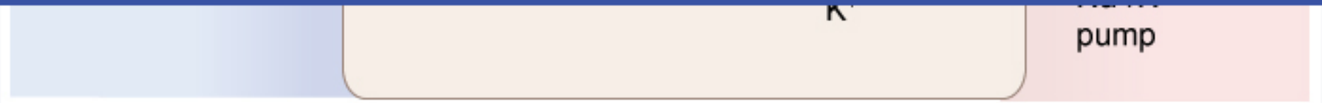
Sodium-glucose cotransporter 2 (SGLT2) is a low-affinity, high-capacity transport protein that is responsible for reabsorbing 90% of filtered glucose in the proximal renal tubule. Glucose reabsorption by SGLT2 is driven by cotransport of sodium, which occurs down its concentration gradient.



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SGLT2 inhibitors (eg, canagliflozin, dapagliflozin) are oral antidiabetic agents that have the following effects:

- Decreased renal reabsorption of glucose, leading to **increased urinary glucose excretion** and lower blood glucose levels
- **Natriuresis** and **osmotic diuresis** due to decreased reabsorption of sodium and glucose, leading to a small **decrease in extracellular fluid volume**, total **body sodium content**, and blood pressure
- Decreased sodium reabsorption and increased sodium delivery to the macula densa, leading to decreased activation of the renin-angiotensin-aldosterone system, lower glomerular (and systemic) pressures, and delayed progression of nephropathy

Educational objective:
Sodium-glucose cotransporter 2 inhibitors decrease renal reabsorption of glucose and sodium, leading to increased urinary glucose excretion and decreased blood glucose levels. In addition, natriuresis and osmotic diuresis lead to a small decrease in extracellular fluid volume, total body sodium content, and blood pressure.

References

- SGLT2 inhibitors with cardiovascular benefits: transforming clinical care in type 2 diabetes mellitus.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 60-year-old man comes to the office for follow-up after a recent emergency department visit due to cough. The patient was diagnosed with acute bronchitis and the symptoms resolved with symptomatic treatment. A chest x-ray obtained during that visit revealed no lung abnormalities, but the bones appeared osteopenic. The patient reports no bone pain and has had no fractures. He has a history of prostate cancer treated with radiation therapy and is taking leuprolide. The patient has no other medical problems and has no known drug allergies. He drinks a glass of wine daily and does not use tobacco or illicit drugs. He eats a balanced diet and exercises regularly. Blood pressure is 120/80 mm Hg and pulse is 80/min. Physical examination shows no abnormalities. A dual-energy x-ray absorptiometry (DXA) scan shows low bone mineral density. Which of the following is the most likely underlying mechanism of the observed finding in this patient?

A. Decreased estrogen and testosterone levels

B. Decreased intestinal calcium absorption

C. Impaired 25-hydroxycholecalciferol activation

D. Increased parathyroid hormone levels

E. Paraneoplastic effects of the cancer cells

Submit

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- ✓ A. Decreased estrogen and testosterone levels (69%)
- B. Decreased intestinal calcium absorption (6%)
- C. Impaired 25-hydroxycholecalciferol activation (6%)
- D. Increased parathyroid hormone levels (5%)
- E. Paraneoplastic effects of the cancer cells (11%)

Omitted
Correct answer
A

69%
Answered correctly

02 secs
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02/12/2020
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Explanation

Antiandrogen therapy

Hypothalamus

Antiandrogen therapy

Hypothalamus
GnRH release

↓

Anterior pituitary
LH release

⊖ GnRH agonists (eg, leuprolide)

↓

Leydig cells
Testosterone synthesis

⊖ Ketoconazole
Spironolactone

↓

Peripheral tissues
Conversion of testosterone to DHT

⊖ 5-alpha reductase inhibitors (eg, finasteride)

↓

Target organs
Androgen receptor-binding

⊖ Flutamide
Cyproterone
Spironolactone

DHT = dihydrotestosterone

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Leuprolide is a **GnRH analog** used to suppress testosterone levels in the treatment of prostate cancer. When administered in a pulsatile fashion, leuprolide has agonist properties; however, long-term leuprolide use results in a continuous GnRH effect (also seen with GnRH infusion) that leads to the downregulation of GnRH receptors on gonadotropin cells in the pituitary gland. This suppresses pituitary LH release and leads to the reduced production of testosterone by Leydig cells. The lower levels of circulating testosterone produce a clinical effect similar to that of surgical orchiectomy.

Hypogonadism can lead to accelerated bone loss and increased risk for **osteoporosis**. In male patients, androgens are aromatized to **estrogens**, which play a large role in bone homeostasis, largely by inhibiting osteoclast-driven cortical bone resorption. Androgens also act on osteoblasts and osteocytes in trabecular (sometimes called cancellous or spongy) bone to preserve bone density.

(Choice B) Glucocorticoids (eg, prednisone) and proton pump inhibitors (eg, omeprazole) are associated with an increased risk of osteoporosis, at least partly due to the decreased intestinal absorption of calcium. GnRH analogs have little effect on intestinal calcium absorption.

(Choices C and D) Elevated parathyroid hormone (PTH) levels stimulate osteoclast activity and release of calcium from bone, increasing the risk of osteoporosis. Similarly, low vitamin D concentrations lead to impaired calcium absorption with a compensatory increase in PTH. Conversion of 25-hydroxyvitamin D (ie, 25-hydroxycholecalciferol) to its active form, 1,25-dihydroxyvitamin D, by 1-alpha-hydroxylase (stimulated by PTH) occurs in the kidneys; this is one of the reasons that patients with chronic kidney disease are at increased risk of osteoporosis. However, this patient does not have a history of chronic kidney disease or hyperparathyroidism, and the vitamin D–PTH axis is not significantly influenced by leuprolide use.

(Choice E) Humoral hypercalcemia of malignancy (HHM) is a paraneoplastic syndrome due to release of PTH-related protein (PTHrP) by malignant cells. PTHrP is structurally similar to PTH and acts on the PTH-1 receptor. HHM is most commonly seen in squamous cell carcinoma (eg, lung), transitional cell carcinomas, and breast and ovarian cancers. It typically presents with severe, symptomatic hypercalcemia (eg, constipation, lethargy) rather than osteoporosis.

Educational objective:
Long-term use of GnRH agonists (eg, leuprolide) suppresses pituitary LH release and leads to the reduced production of testosterone. The lower levels of circulating testosterone produce a clinical effect similar to that of surgical orchiectomy and can lead to accelerated bone loss and increased risk for osteoporosis.

References

estrogens, which play a large role in bone homeostasis, largely by inhibiting osteoclast-driven cortical bone resorption. Androgens also act on osteoblasts and osteocytes in trabecular (sometimes called cancellous or spongy) bone to preserve bone density.

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Long-term use of GnRH agonists (eg, leuprolide) suppresses pituitary LH release and leads to the reduced production of testosterone. The lower levels of circulating testosterone produce a clinical effect similar to that of surgical orchiectomy and can lead to accelerated bone loss and increased risk for osteoporosis.

References

- Bone health management in prostate cancer patients receiving androgen deprivation therapy.

Pharmacology	Endocrine, Diabetes & Metabolism	Osteoporosis
Subject	System	Topic

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A 29-year-old nulligravid woman comes to the office due to a 2-month history of worsening bilateral nipple discharge that stains her bra. The patient has felt no breast mass and has had no breast pain, headaches, or vision changes. Her last menstrual period was 3 months ago, and home pregnancy tests have been negative. Previously, she had regular menstrual cycles at 28-day intervals. The patient has no other medical conditions and takes no medications. Vital signs are within normal limits. On physical examination, visual fields are intact by confrontation. A whitish fluid can be expressed bilaterally on nipple compression. There are no breast masses or lymphadenopathy. Pelvic examination reveals no abnormalities. Serum beta-hCG testing is negative. Brain imaging shows a 0.6-cm pituitary mass. Pharmacotherapeutic treatment is begun, and on a follow-up visit the patient reports that her symptoms are improving. Which of the following is the most likely mechanism of action of this medication?

- A. Increased estrogen effect on the pituitary
- B. Inhibition of gonadotropin-releasing hormone secretion
- C. Inhibition of hypothalamic dopaminergic neurons
- D. Stimulation of pituitary dopamine receptors
- E. Stimulation of thyrotropin-releasing hormone receptors

Submit

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- A. Increased estrogen effect on the pituitary (1%)
- B. Inhibition of gonadotropin-releasing hormone secretion (4%)
- C. Inhibition of hypothalamic dopaminergic neurons (8%)
- ✓ D. Stimulation of pituitary dopamine receptors (84%)
- E. Stimulation of thyrotropin-releasing hormone receptors (1%)

Omitted
Correct answer
D

84%
Answered correctly

01 sec
Time Spent

02/16/2020
Last Updated

Explanation

Prolactinoma	

Prolactinoma	
Clinical features	• **Premenopausal women**: Oligomenorrhea/amenorrhea, infertility, galactorrhea, hot flashes, decreased bone density • **Postmenopausal women**: Mass-effect symptoms (headache, visual field defects) • **Men**: Infertility, decreased libido, impotence, gynecomastia
Laboratory/ imaging	• Serum prolactin (often >200 ng/mL) • Tests to rule out renal insufficiency (creatinine) & hypothyroidism (TSH, thyroxine) • MRI of the brain/pituitary
Treatment	• Dopamine agonist (cabergoline) • Trans-sphenoidal surgery

Galactorrhea is abnormal secretion of breast milk not associated with pregnancy or breastfeeding. It is most commonly due to excess prolactin, which directly stimulates milk secretion in the breasts. Pituitary lactotroph adenomas (**prolactinomas**) can cause very high prolactin levels and are a common cause of galactorrhea.

Unlike most pituitary hormones, which are under positive regulation by releasing hormones from the hypothalamus, prolactin is primarily under negative regulation by hypothalamic dopaminergic neurons via the pituitary stalk. Because of the tonic inhibitory effect of dopamine on prolactin secretion, **dopamine agonists** (eg, cabergoline, bromocriptine) can be used to treat hyperprolactinemia. Dopamine agonist therapy reduces adenoma size, suppresses prolactin production, and, in patients with small (<1 cm, as in this patient) prolactinomas and no mass-effect symptoms (eg, headache, visual field defects), can often induce a prolonged clinical response.

(Choices A and C) Estrogen stimulates prolactin gene transcription and secretion. Strongly estrogenic medications (eg, birth control pills) can potentially worsen rather than alleviate galactorrhea. Dopamine antagonists (eg, antipsychotics) directly increase prolactin secretion and also can worsen galactorrhea.

(Choice B) Hyperprolactinemia causes amenorrhea in women due to the inhibitory effect of prolactin on hypothalamic GnRH release. Dopaminergic medications suppress prolactin secretion and can restore normal GnRH secretion.

(Choice E) Thyrotropin-releasing hormone (TRH) stimulates secretion of prolactin by lactotrophs, although its role in regulating prolactin release

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(Choice E) Thyrotropin-releasing hormone (TRH) stimulates secretion of prolactin by lactotrophs, although its role in regulating prolactin release is secondary to the inhibition of prolactin secretion by dopamine. Factors that increase TRH release would worsen hyperprolactinemia.

Educational objective:
Galactorrhea is abnormal secretion of breast milk not associated with pregnancy or breastfeeding. It is most commonly due to excess prolactin, as seen in prolactin-secreting pituitary adenomas. Prolactin is under negative regulation by hypothalamic dopaminergic neurons, and dopamine agonists can be used to treat hyperprolactinemia.

References

- Evaluation and management of galactorrhea.

Pharmacology	Endocrine, Diabetes & Metabolism	Pituitary adenoma
Subject	System	Topic

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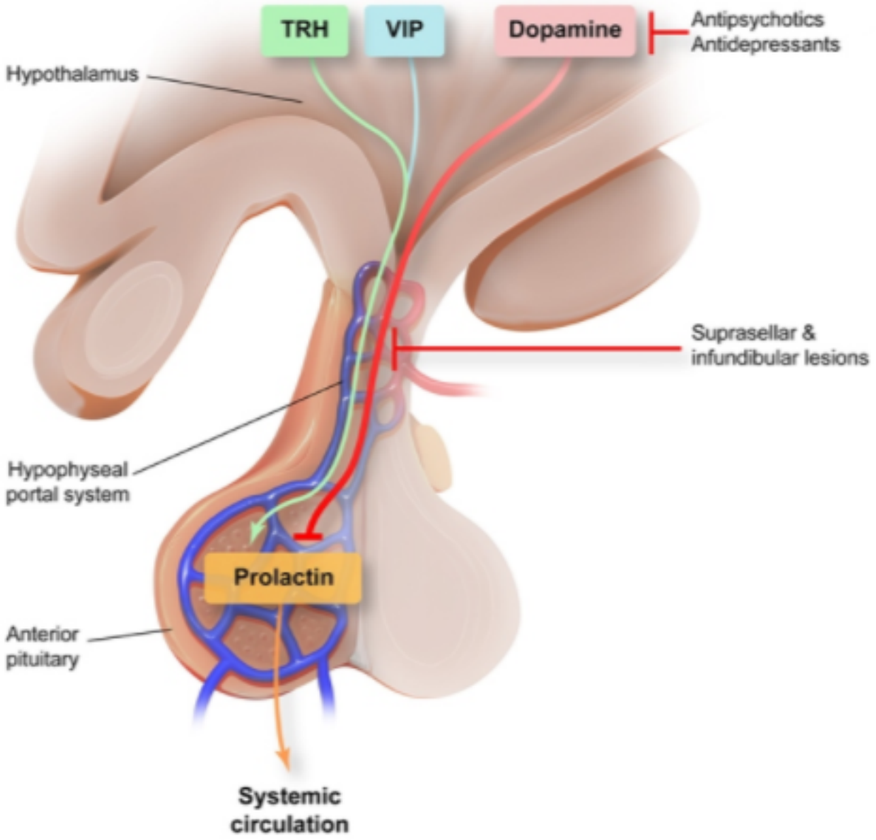
which directly stimulates milk secretion in the breasts. Pituitary lactotroph adenomas (**prolactinomas**) can cause very high prolactin levels and

Exhibit Display

Prolactin



TRH = thyrotropin-releasing hormone; VIP = vasoactive intestinal peptide.

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A 56-year-old man with type 2 diabetes mellitus, hypertension, and hyperlipidemia comes to the office due to elevated blood glucose levels. The patient's current medications include metformin, lisinopril, and simvastatin. Blood pressure is 150/90 mm Hg and pulse is 88/min. BMI is 37 kg/m^2. Physical examination is unremarkable. Laboratory studies show a fasting glucose level of 156 mg/dL, serum creatinine of 1.1 mg/dL, hemoglobin A1c of 8.1%, and urine albumin-creatinine ratio of 200 mg/g (normal: <30). Treatment with empagliflozin is initiated. Which of the following effects is most likely to be seen with this new treatment?

A. Decrease in gastrointestinal absorption of glucose

B. Increase in body weight

C. Increase in endogenous insulin production

D. Reduction in glomerular hyperfiltration

E. Suppression of glucagon secretion

Submit

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A. Decrease in gastrointestinal absorption of glucose (19%)

B. Increase in body weight (7%)

C. Increase in endogenous insulin production (5%)

✓ D. Reduction in glomerular hyperfiltration (61%)

E. Suppression of glucagon secretion (5%)

Omitted
Correct answer
D

61%
Answered correctly

02 secs
Time Spent

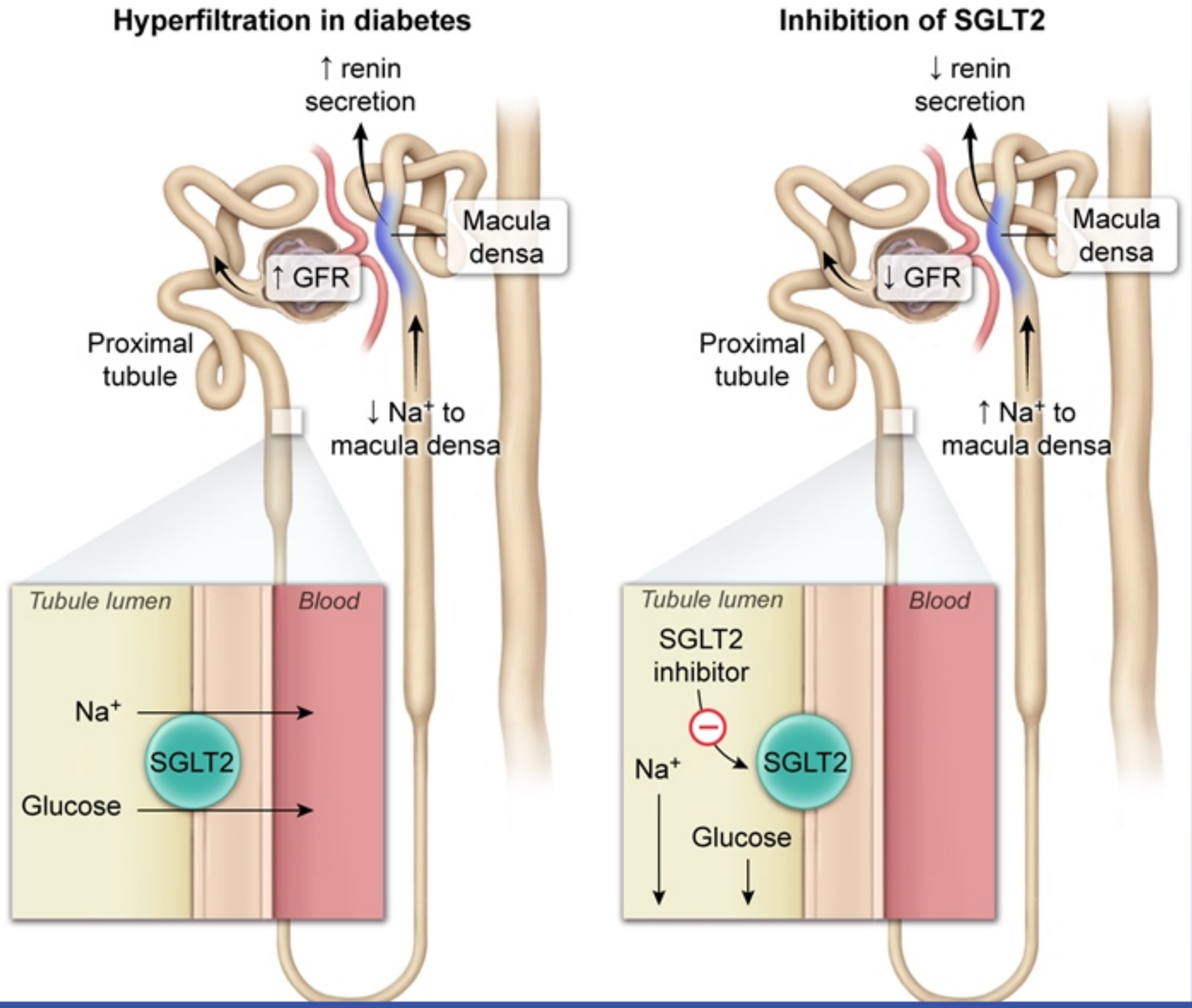
06/09/2020
Last Updated

Explanation

SGLT2 and renal hyperfiltration

Hyperfiltration in diabetes	Inhibition of SGLT2
↑ renin secretion	↓ renin secretion

SGLT2 and renal hyperfiltration



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This patient has incipient **diabetic nephropathy** with moderately increased albuminuria (ie, 30-300 mg/g). Although patients with more advanced diabetic kidney disease typically have reduced glomerular filtration (rising serum creatinine), in earlier stages, filtration is normal to increased and serum creatinine may be normal.

In the kidneys, filtered glucose is normally reabsorbed with sodium by **sodium-glucose cotransporter 2 (SGLT2)** in the proximal tubule. In patients with diabetes, the excess filtered glucose load causes increased reabsorption of sodium by SGLT2. This results in decreased sodium delivery to the macula densa, stimulating renin secretion by the juxtaglomerular apparatus and, ultimately, increasing angiotensin II levels. Angiotensin II induces relative vasoconstriction in the renal efferent arterioles, increasing hydrostatic pressure in the glomerular capillaries and causing **hyperfiltration**.

SGLT2 inhibitors (eg, empagliflozin) decrease the reabsorption of glucose and sodium in the proximal tubule, causing urine glucose wasting and lowering blood glucose. They also increase sodium delivery to the macula densa, which leads to decreased renin secretion, lower glomerular pressures, **reduced hyperfiltration**, and delayed progression of nephropathy.

(Choice A) Glucose is absorbed in the intestine primarily via SGLT1 (not SGLT2), which is not significantly affected by empagliflozin.

(Choices B and C) Most patients on SGLT2 inhibitors experience modest weight loss, not gain, due to urinary glucose wasting and lower circulating insulin levels. SGLT2 inhibitors lower blood glucose, leading to decreased secretion of insulin by pancreatic beta cells.

(Choice E) SGLT2 inhibitors are associated with increased, not suppressed, glucagon secretion, possibly due to lower glucose and insulin levels or a direct effect on pancreatic alpha cells.

Educational objective:
In patients with diabetes, excess glucose in the proximal tubule causes increased reabsorption of sodium by sodium-glucose cotransporter 2 (SGLT2). This leads to decreased delivery of sodium to the macula densa and increased secretion of renin, ultimately increasing glomerular filtration pressure and causing hyperfiltration. SGLT2 inhibitors increase the delivery of sodium to the macula densa, decreasing renin production and reducing hyperfiltration.

References

- SGLT2 inhibition and kidney protection.

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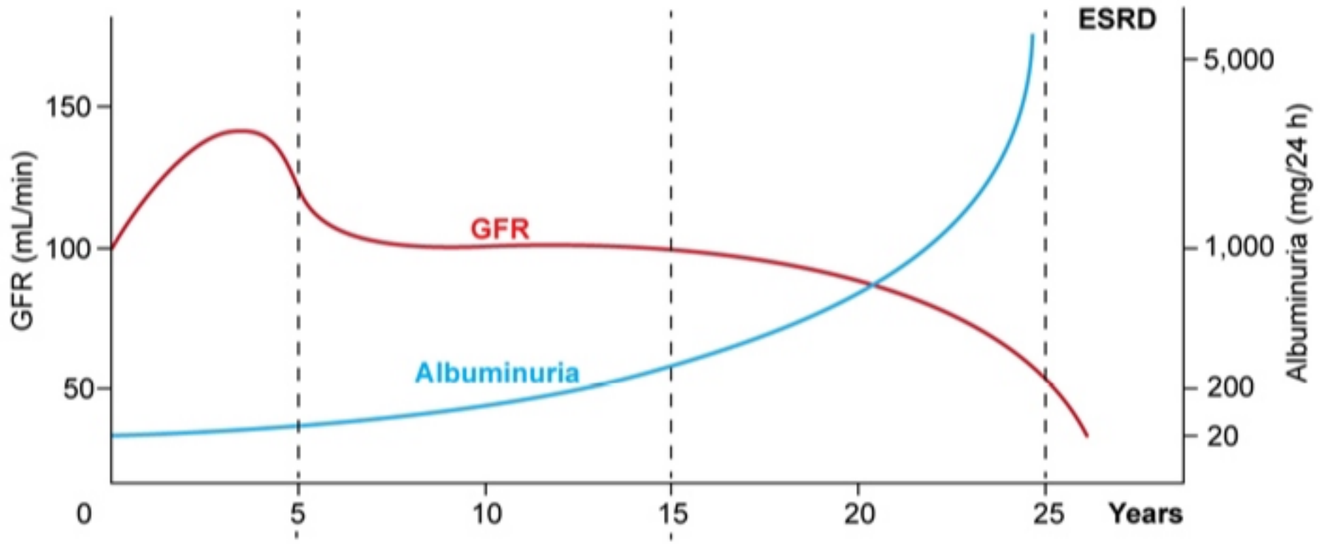
Natural history of diabetic nephropathy



Hyperfiltration
- Glomerular hypertrophy
- ↑ GFR

Incipient DN
- Mesangial expansion, glomerular basement membrane thickening, arteriolar hyalinosis
- Moderately increased albuminuria
- Hypertension

Overt DN
- Mesangial nodules (Kimmelstiel-Wilson lesion), tubulointerstitial fibrosis
- Overt proteinuria
- Nephrotic syndrome
- ↓ GFR

DN = diabetic nephropathy; **ESRD** = end-stage renal disease; **GFR** = glomerular filtration rate.

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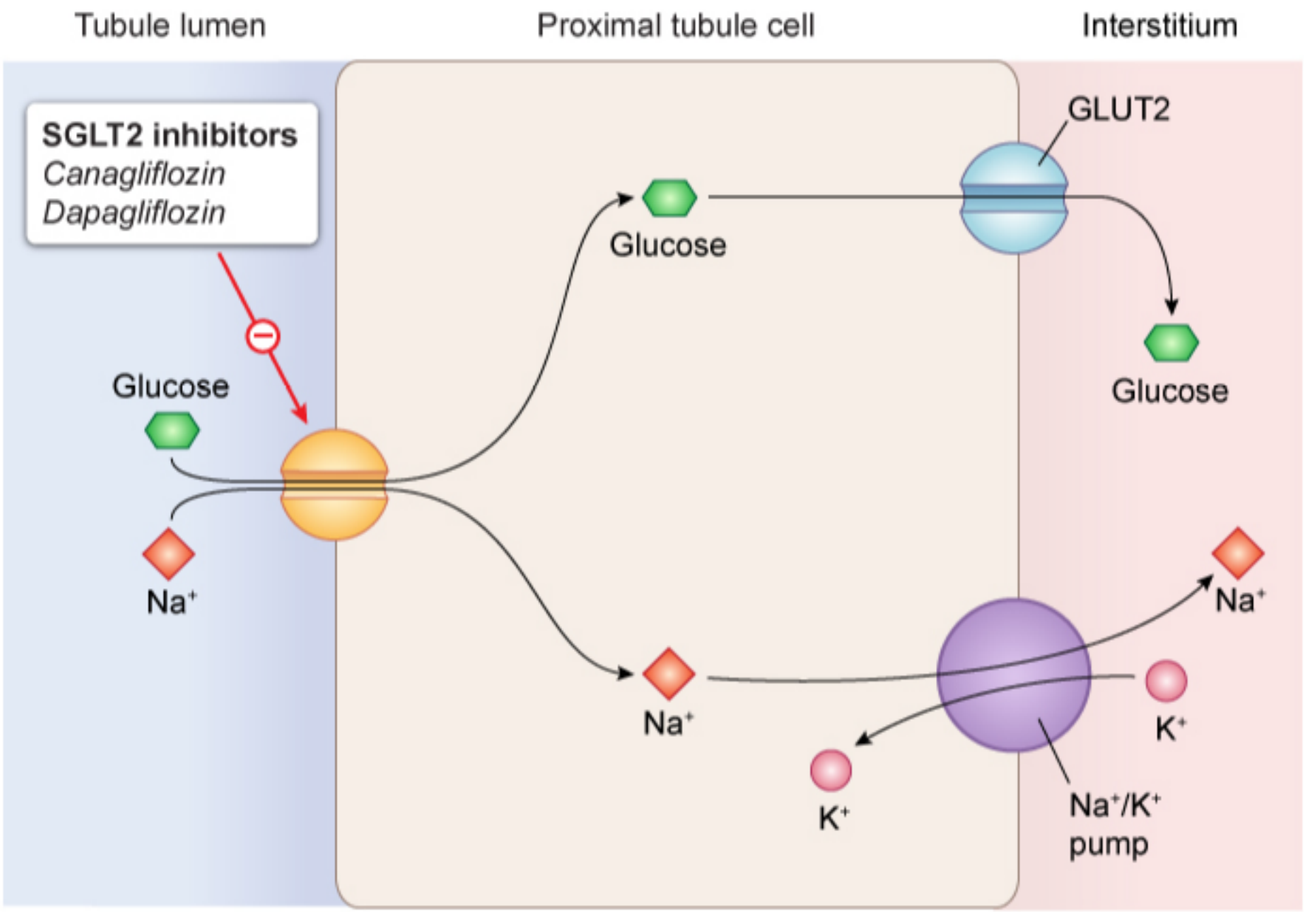
SGLT2 inhibitors



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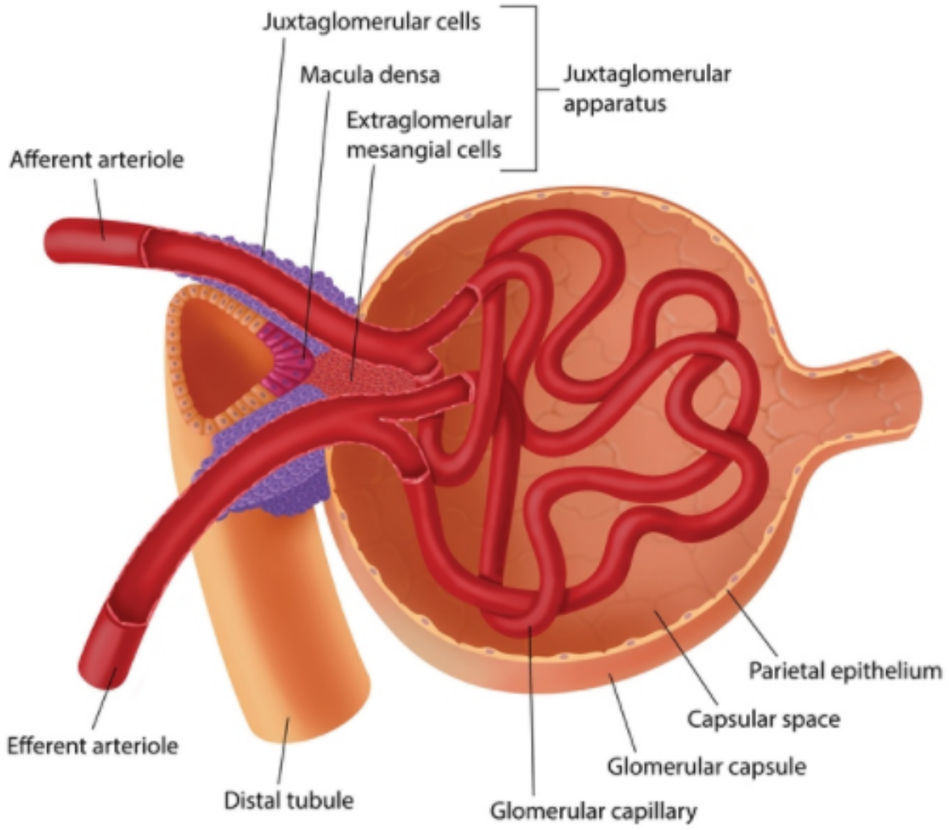
Juxtaglomerular apparatus



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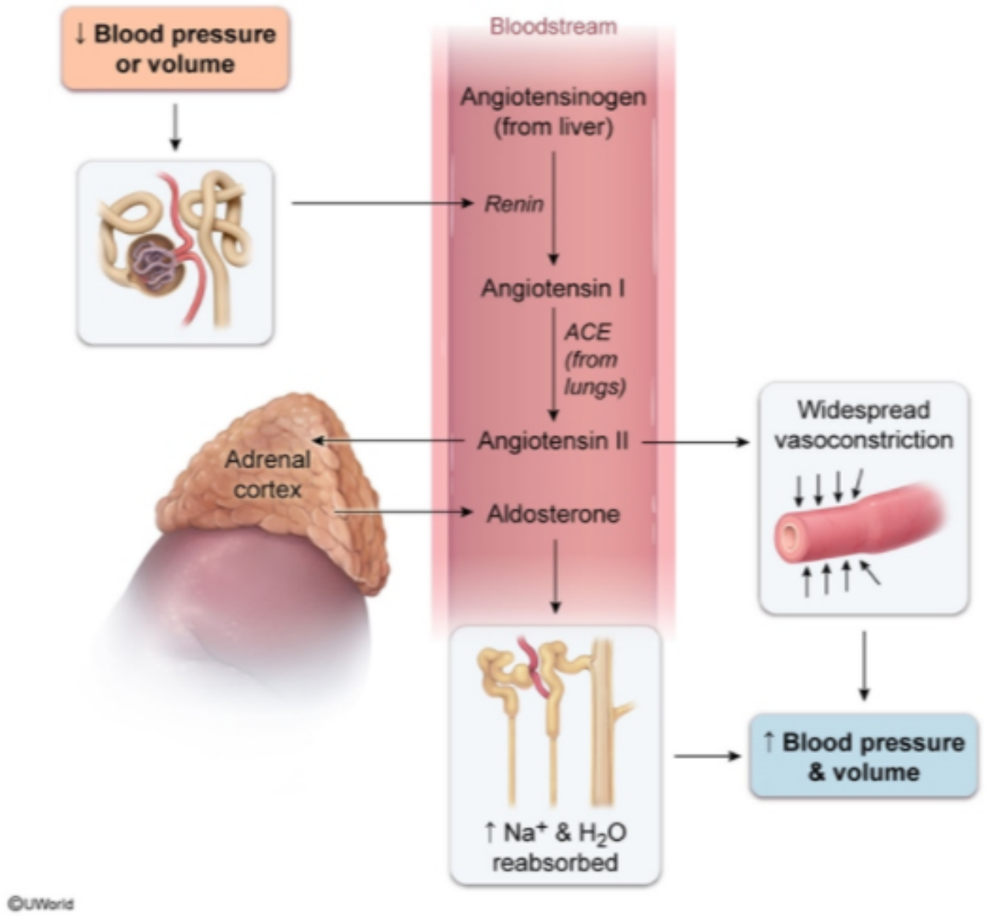
Renin-angiotensin-aldosterone system



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In the kidneys, filtered glucose is normally reabsorbed with sodium by **sodium-glucose cotransporter 2 (SGLT2)** in the proximal tubule. In patients with diabetes, the excess filtered glucose load causes increased reabsorption of sodium by SGLT2. This results in decreased sodium delivery to the macula densa, stimulating renin secretion by the juxtaglomerular apparatus and, ultimately, increasing angiotensin II levels. Angiotensin II induces relative vasoconstriction in the renal efferent arterioles, increasing hydrostatic pressure in the glomerular capillaries and causing **hyperfiltration**.

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References

- SGLT2 inhibition and kidney protection.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetic nephropathy
Subject	System	Topic

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A 65-year-old woman comes to the emergency department due to left leg pain and swelling for the past day. She has had no trauma or fever. The patient has a history of hypertension, congestive heart failure, type 2 diabetes mellitus, and osteoporosis. Family history is notable for breast cancer in her mother and sister. She takes multiple medications. Temperature is 37.8 C (100 F), blood pressure is 130/80 mm Hg, and pulse is 99/min. Pulse oximetry shows 98% on ambient air. The lungs are clear to auscultation, and heart sounds are normal without murmur. There is tenderness and edema of the left lower extremity up to the mid thigh. Venous Doppler ultrasonography reveals an occluding thrombus in the left femoral and popliteal veins. Which of the following pharmacotherapies most likely contributed to this patient's current condition?

- A. Alendronate
- B. Chlorthalidone
- C. Empagliflozin
- D. Liraglutide
- E. Raloxifene
- F. Sacubitril-valsartan
- G. Spironolactone

Submit

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- A. Alendronate (7%)
- B. Chlorthalidone (6%)
- C. Empagliflozin (2%)
- D. Liraglutide (2%)
- ✓ E. Raloxifene (72%)
- F. Sacubitril-valsartan (3%)
- G. Spironolactone (4%)

Omitted
Correct answer
E

72%
Answered correctly

02 secs
Time Spent

02/16/2020
Last Updated

Explanation

Selective estrogen receptor modulators

Selective estrogen receptor modulators	
Drugs	• Tamoxifen • Raloxifene
Mechanism of action	• Competitive inhibitor of estrogen binding • Mixed agonist/antagonist action
Indications	• Prevention of breast cancer in high-risk patients • Tamoxifen: adjuvant treatment of breast cancer • Raloxifene: postmenopausal osteoporosis
Adverse effects	• Hot flashes • Venous thromboembolism • Endometrial hyperplasia & carcinoma (tamoxifen only)

Selective estrogen receptor modulators (SERMs), such as raloxifene and tamoxifen, are nonsteroidal compounds that bind to estrogen receptors and exhibit estrogen antagonist and agonist properties in a tissue-specific manner. **Raloxifene** has estrogen agonist activity on bone, inhibiting bone resorption and improving bone mineral density while exhibiting estrogen antagonist activity in the breast and endometrial tissue.

Medicines with estrogen agonist activity, including SERMs, oral contraceptives, and hormone replacement therapy, cause a prothrombotic state and can increase the risk for **venous thromboembolism** (VTE). Proposed mechanisms include increased levels of clotting factors (eg, prothrombin; fibrinogen; factor VII, VIII, X) and activated protein C resistance. Current or prior thromboembolic disorders are contraindications to SERM use.

(Choice A) Bisphosphonates (eg, alendronate) inhibit osteoclast-mediated bone resorption. Side effects include hypocalcemia, esophagitis, and osteonecrosis of the jaw. Bisphosphonates have no estrogenic activity and do not increase the risk for VTE.

(Choice B) Thiazide diuretics (eg, chlorthalidone) inhibit Na^+/Cl^- cotransporters in the distal convoluted tubule, decreasing reabsorption of Na^+ and increasing reabsorption of calcium, which can be beneficial in patients with osteoporosis. Side effects include electrolyte abnormalities, hyperglycemia, and hyperlipidemia.

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(Choice C) Sodium-glucose cotransporter 2 inhibitors (eg, empagliflozin) reduce reabsorption of glucose in the proximal renal tubule, leading to urinary glucose excretion. Side effects include urinary tract and genital mycotic infections as well as hypotension.

(Choice D) Glucagon-like peptide-1 (GLP-1) is released by the small intestine in response to food and induces glucose-dependent insulin release from pancreatic beta cells. GLP-1 agonists (eg, liraglutide) lower blood glucose with little hypoglycemia risk, but can cause gastrointestinal upset and weight loss.

(Choice F) Sacubitril is a neprilysin inhibitor that increases atrial natriuretic peptide and brain natriuretic peptide levels (thereby promoting diuresis and vasodilation) in patients with heart failure. It is administered with an angiotensin II receptor blocker (valsartan) to offset the associated increase in angiotensin II levels. Side effects include cough, hyperkalemia, and renal impairment.

(Choice G) Spironolactone is an aldosterone antagonist used in patients with heart failure. It has prominent anti-androgenic effects, which can lead to gynecomastia in male patients due to unopposed estrogenic effects on breast tissue. However, it has minimal effects on estrogen levels and does not increase the risk of VTE.

Educational objective:

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(Choice D) Glucagon-like peptide-1 (GLP-1) is released by the small intestine in response to food and induces glucose-dependent insulin release from pancreatic beta cells. GLP-1 agonists (eg, liraglutide) lower blood glucose with little hypoglycemia risk, but can cause gastrointestinal upset and weight loss.

(Choice F) Sacubitril is a neprilysin inhibitor that increases atrial natriuretic peptide and brain natriuretic peptide levels (thereby promoting diuresis and vasodilation) in patients with heart failure. It is administered with an angiotensin II receptor blocker (valsartan) to offset the associated increase in angiotensin II levels. Side effects include cough, hyperkalemia, and renal impairment.

(Choice G) Spironolactone is an aldosterone antagonist used in patients with heart failure. It has prominent anti-androgenic effects, which can lead to gynecomastia in male patients due to unopposed estrogenic effects on breast tissue. However, it has minimal effects on estrogen levels and does not increase the risk of VTE.

Educational objective:
Raloxifene is a selective estrogen receptor modulator (SERM) that has estrogen agonist activity on bone and decreases bone resorption. Medicines with estrogen agonist activity, including SERMs, oral contraceptives, and hormone replacement therapy, can increase the risk for venous thromboembolism.

References

- Selective estrogen receptor modulators in menopause.

Pharmacology	Endocrine, Diabetes & Metabolism	Osteoporosis
Subject	System	Topic

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A 65-year-old woman comes to the clinic for follow up of type 2 diabetes mellitus. Medical history is notable for hypertension, stable coronary artery disease, and heart failure with preserved ejection fraction. Blood pressure is 144/95 mm Hg. Physical examination shows no murmurs, and the lungs are clear on auscultation. Fasting glucose is 122 mg/dL and hemoglobin A1c is 7.8%. The remainder of the laboratory results, including hepatic and renal markers, are normal. The patient is given a prescription for canagliflozin. She should be counseled on which of the following potential complications prior to initiation of this medication?

A. Fluid overload

B. Hypoglycemia

C. Lactic acidosis

D. Urinary infection

E. Weight gain

Submit

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- A. Fluid overload (1%)
- B. Hypoglycemia (4%)
- C. Lactic acidosis (0%)
- ✓ D. Urinary infection (90%)
- E. Weight gain (2%)

Omitted
Correct answer
D

90%
Answered correctly

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Time Spent

05/27/2020
Last Updated

Explanation

Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	**Mechanism of action**	**Side effects**
Insulin secretagogues		• Hypoglycemia

Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	**Mechanism of action**	**Side effects**
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
Biguanides • Metformin	Stimulate AMPK & inhibit mitochondrial gluconeogenesis, ↓ hepatic glucose production & ↑ peripheral glucose uptake	• Diarrhea • Lactic acidosis
Thiazolidinediones • Pioglitazone	Activate transcription regulator PPAR-γ, ↓ insulin resistance	• Fluid retention/heart failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
α-glucosidase inhibitors • Acarbose • Miglitol	↓ Intestinal disaccharide absorption	• Diarrhea • Flatulence
SGLT2 inhibitors • Canagliflozin	↑ Renal glucose excretion	• Urinary tract infections

		• Weight gain
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α-glucosidase inhibitors • Acarbose • Miglitol	↓ Intestinal disaccharide absorption	• Diarrhea • Flatulence
SGLT2 inhibitors • Canagliflozin • Dapagliflozin	↑ Renal glucose excretion	• Urinary tract infections • Hypotension
AMPK = adenosine monophosphate–activated protein kinase; **DPP4** = dipeptidyl peptidase-4; **GIP** = gastric inhibitory polypeptide; **GLP-1** = glucagonlike peptide-1; K_{ATP} = ATP-sensitive potassium; **PPAR-γ** = peroxisome proliferator–activated receptor γ; **SGLT2** = sodium-glucose cotransporter 2.		

Sodium-glucose cotransporter 2 (SGLT2) is a high-capacity transport protein that reabsorbs 90% of filtered glucose in the proximal tubule. **SGLT2 inhibitors** (eg, canagliflozin, dapagliflozin) are oral antidiabetic agents that decrease renal reabsorption of glucose, leading to urinary glucose loss and decreased blood glucose levels. The decreased reabsorption of sodium and glucose also induces **osmotic diuresis**, leading to a decrease in blood pressure and a lower rate of hospitalization for heart failure.

However, the glycosuria induced by SGLT2 inhibitors creates a more favorable environment for pathogenic bacteria and fungi in the genitourinary tract and perineum. This leads to an increased risk for **urinary tract infections** (eg, pyelonephritis), **genital mycotic infections** (eg, vaginitis), and **necrotizing fasciitis** of the perineum (Fournier gangrene). Other adverse effects include hypovolemia, which can lead to orthostatic hypotension and acute kidney injury.

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(Choice A) Thiazolidinediones (eg, pioglitazone) increase the reabsorption of sodium in the renal collecting tubule; this can lead to significant fluid retention, particularly in patients with heart failure. In contrast, SGLT2 inhibitors reduce fluid retention.

(Choices B and E) Exogenous insulin and sulfonylureas, which stimulate endogenous insulin secretion, can cause hypoglycemia and weight gain. SGLT2 inhibitors carry a low risk of hypoglycemia because the glucose-lowering effect is proportionate to the filtered glucose load; also, renal glucose wasting typically induces mild weight loss.

(Choice C) Metformin inhibits hepatic gluconeogenesis, leading to the accumulation of lactate. Patients with decreased lactate clearance (eg, renal or hepatic dysfunction, congestive heart failure) can have excessive accumulation of lactate, leading to lactic acidosis.

Educational objective:
Sodium-glucose cotransporter 2 inhibitors (eg, canagliflozin, dapagliflozin) decrease renal reabsorption of glucose, leading to urinary glucose loss and decreased blood glucose levels. However, the resulting glycosuria can lead to genitourinary tract infections and necrotizing fasciitis of the perineum.

References

- Risks associated with SGLT2 inhibitors: an overview.

Pharmacology	Endocrine, Diabetes & Metabolism	Antidiabetic drugs
Subject	System	Topic

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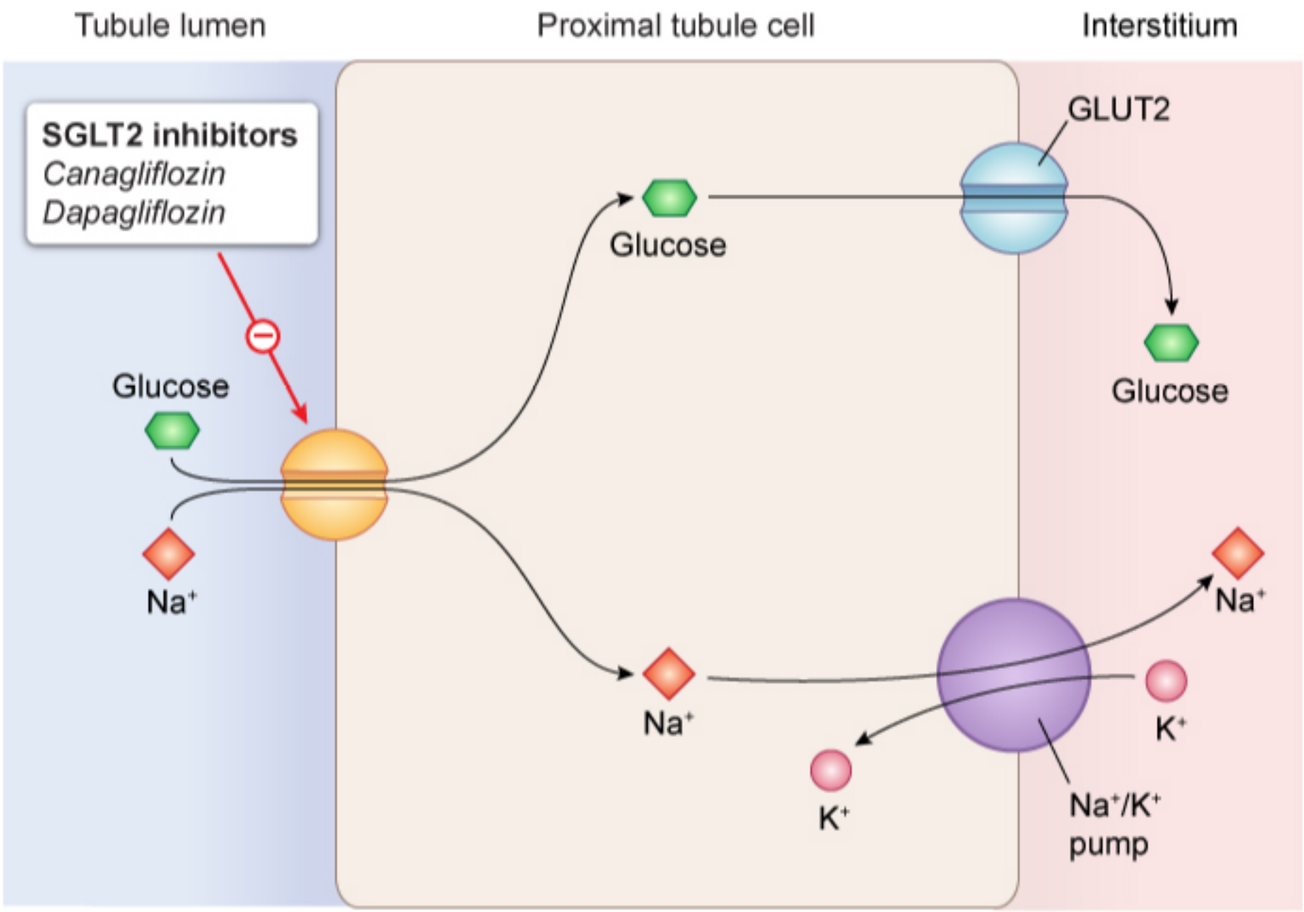
Sodium-glucose cotransporter 2 (SGLT2) is a high capacity transport protein that reabsorbs 90% of filtered glucose in the proximal tubule.

Exhibit Display

SGLT2 inhibitors



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A 40-year-old man comes to the office due to erectile dysfunction and loss of libido. The patient's history is notable for Hodgkin lymphoma that was treated with chemotherapy. Physical examination is normal except for small testes. Laboratory evaluation shows consistently low total and free early morning testosterone levels and elevated serum LH. Transdermal testosterone therapy is prescribed. Which of the following should be periodically monitored during this patient's treatment?

A. ECG

B. Hematocrit

C. Serum cortisol

D. Serum creatinine

E. Serum TSH and thyroxine

Submit

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- A. ECG (5%)
- ✓ B. Hematocrit (48%)
- C. Serum cortisol (22%)
- D. Serum creatinine (6%)
- E. Serum TSH and thyroxine (16%)

Omitted
Correct answer
B

48%
Answered correctly

02 secs
Time Spent

05/09/2020
Last Updated

Explanation

Testosterone replacement therapy	
Indications	• Symptoms of hypogonadism • Consistently low serum testosterone
Contraindications	• Prostate cancer (elevated PSA) • Hematocrit >50%

Testosterone replacement therapy	
Indications	• Symptoms of hypogonadism • Consistently low serum testosterone
Contraindications	• Prostate cancer (elevated PSA) • Hematocrit >50% • Severe obstructive sleep apnea
Adverse effects	• Erythrocytosis • Venous thromboembolism

PSA = prostate-specific antigen.

This patient has **hypogonadism** presenting with erectile dysfunction and loss of libido associated with a low serum testosterone level. Other common manifestations of hypogonadism include fatigue, loss of muscle mass, and decreased bone density. Hypogonadism is a common complication of cytotoxic chemotherapy (eg, cyclophosphamide) in long-term cancer survivors. **Testosterone replacement therapy** (TRT) is indicated for men with symptoms of hypogonadism and persistently low serum testosterone levels.

However, testosterone has trophic effects on the prostate, mediated by conversion to dihydrotestosterone by 5-alpha reductase in local tissues. TRT is associated with increased prostate volume, a rise in serum **prostate-specific antigen** (PSA), and a possible increase in the risk for prostate cancer. PSA should be measured prior to initiation of therapy and periodically thereafter.

In addition, TRT can induce **erythrocytosis**, possibly due to suppression of hepcidin and increased intestinal iron absorption. This can lead to increased blood viscosity and an elevated risk for thromboembolism. Therefore, TRT should not be initiated in patients with a baseline hematocrit >50%, and **hematocrit** should be followed regularly during treatment.

(Choice A) Some experts believe there is an increased risk of cardiovascular events associated with TRT and patients should be advised of this possibility. However, testing (eg, ECG) in asymptomatic patients is not necessary.

(Choices C and E) Patients with central/secondary hypogonadism (ie, low testosterone with low or inappropriately normal LH) should be tested

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(Choices C and E) Patients with central/secondary hypogonadism (ie, low testosterone with low or inappropriately normal LH) should be tested for deficiencies in other hypothalamic-pituitary systems (eg, TSH + serum thyroxine, morning cortisol). However, this patient has an elevated LH level consistent with primary hypogonadism, making these additional tests unnecessary.

(Choice D) Because renal toxicity is not a major concern with TRT, renal function does not need to be monitored.

Educational objective:
Testosterone replacement therapy is indicated for men with symptomatic hypogonadism. It is associated with an increase in serum prostate-specific antigen and may raise the risk of prostate cancer. In addition, testosterone therapy can cause erythrocytosis (leading to thromboembolism), and hematocrit should be regularly monitored.

References

- Erythrocytosis following testosterone therapy.
- Hypogonadism in male cancer patients.

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Pharmacology	Endocrine, Diabetes & Metabolism	Male sexual dysfunction
Subject	System	Topic

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